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BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 17 1949

CRYSTALLINE ANTI-PERNICIOUS-ANAEMIA FACTOR

BY

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The anti-pernicious-anaemia factor (vitamin B_{12}) having at last been isolated in the pure crystalline state, it may reasonably be asked why this took so long. Within a few weeks of one another, independent announcements of the achievement were made by American and British teams (Rickes *et al.*, 1948a ; Lester Smith and Parker, 1948). Yet it is twenty-two years since Minot and Murphy (1926) first discovered the effectiveness of liver therapy for pernicious anaemia. During the intervening years many new vitamins and hormones have been discovered, and nearly all of them have been concentrated, purified, and analysed and have had their chemical constitutions elucidated and confirmed by synthesis. All the well-defined vitamins have been prepared synthetically with the partial exception of vitamins D_2 and D_3, which have been "synthesized" only from biologically inert natural sterols.

In the light of these achievements the fact that the anti-pernicious-anaemia factor still remained to be isolated became an increasing challenge to biochemists. The delay was certainly not due to lack of interest in the problem. In a review on the factor published in 1945 SubbaRow, Hastings, and Elkin were able to cite no fewer than 129 relevant references.

The prime necessity for successful isolation of a natural biologically active substance is a means for its assay. The quicker and the more reliable the assay method the more rapid is progress likely to be, because there is usually no great difficulty in devising fractionation techniques that may be applicable. Indeed, for the water-soluble vitamins there are available a number of techniques that have become almost standard practice. One recalls, for example, such methods as precipitation with salts of lead, silver, and mercury, fractionation of phosphotungstates, adsorption on charcoal, and so on. For all the vitamins that were isolated within a short period of their initial discovery satisfactory tests were available. Thus, aneurin could be assayed by growth-rate methods, using rats ; riboflavin could be assayed very easily by its intense fluorescence in ultra-violet light ; ascorbic acid even more easily by titration with iodine or still more specific oxidizing agents.

For the anti-pernicious-anaemia factor, however, the only available test until very recently was the assay on clinical cases. Moreover, only a small fraction of these cases were suitable for assay purposes. Much ingenuity was expended in attempting to devise animal tests, but until very recently none of them has proved reliable. It now seems that it may be possible to base an assay technique on the observation that chicks need the factor. The American workers (Rickes *et al.*, 1948a) had the advantage of a microbiological assay technique with *Lactobacillus lactis* Dorner (Shorb, 1948), but the news of this came too late to be of any assistance to our British team. Thus an adequate number of clinical tests was vital to the success of the work. It is probably true to say that no previous investigator in this field had the advantage of so many carefully conducted clinical tests as we were afforded by our collaborator, Dr. C. C. Ungley.

A Review of Earlier Work

The more outstanding contributions to the chemical fractionation of liver are perhaps worth reviewing again in the light of present knowledge. The first important advances were made by Cohn, Minot, *et al.* (1928). They showed that the factor could be extracted from liver with water at faintly acid *p*H, and that proteins could be removed and other impurities separated by addition of alcohol to about 70% concentration. After evaporation to small bulk the active fraction could be thrown out with strong alcohol : this was the famous "Cohn's fraction G." This insolubility in alcohol was due to co-precipitation with other substances present in the crude extract, because at a later stage of purification the factor became soluble in alcohol. Cohn, Minot, *et al.* also showed that the active principle was precipitated by phosphotungstic acid but not by lead acetate, and that it could be extracted with butanol.

These techniques were successfully used again by West and Nichols (1928). West and Howe (1930) claimed the isolation of an active crystalline quinine salt, but later they withdrew this claim.

Dakin and West (1935) and Dakin, Ungley, and West (1936) reported an extensive investigation in which a number of new procedures were developed. They showed that impurities could be precipitated with alcoholic calcium acetate, and that the active principle could be precipitated with Reinecke acid and also with uranium acetate. They showed, too, that the factor could be salted out from neutral solutions by ammonium or magnesium sulphate, and from acid solution by sodium chloride.

New Techniques

Valuable new techniques were introduced in 1936 by Laland and Klem. They reported that the active factor could be extracted from aqueous solutions with liquefied phenol and also that it could be adsorbed on activated charcoal and eluted with liquefied phenol.

By the repeated use of these procedures, together with salting out by ammonium sulphate and fractionation with alcohol and ether, they obtained fractions reported by Strandell to be clinically active in doses of a milligram or so. These remarkable claims were received initially with some scepticism, especially as the novel techniques introduced were not described in sufficient detail to permit exact replication by independent workers. Moreover, when the use of techniques alleged to be those of Laland and Klem, but in effect not closely similar, led to the

separation of much less active fractions, there was a tendency to discredit the Norwegian workers. Thus they have never received proper recognition for genuine achievements that were not bettered during the next ten years. Moreover, their description of their most active fraction as a bright reddish-yellow substance acquires new significance in the light of present knowledge.

We were accorded the privilege of examining their case reports at the time; although in several instances the responses were inadequate with the very small doses given, there seemed no doubt that the fractions tested were very much more active than anything previously obtained. In addition, we were able to secure independent clinical tests on some of their less highly purified fractions, which proved fully active in single doses of less than 10 mg. It should be added that their methods of fractionation have provided an invaluable foundation for our own work. Karrer and his colleagues (1938) also reported the preparation of fractions fully active in doses of 10 mg., or rather less, by methods that were not described in detail.

It is difficult to assess the work of Jacobson, SubbaRow, and others published between 1935 and 1938 (see SubbaRow *et al.*, 1945). These workers claimed that successful treatment of pernicious anaemia called for the simultaneous administration of several factors. One of these was identified as *l*-tyrosine, but the others were not fully purified. Their theory was supported by a reasonable weight of clinical evidence, but it has not been widely accepted. Ungley has now presented ample evidence showing that the pure crystalline anti-pernicious-anaemia factor alone, in adequate doses, gives a classical response in cases of pernicious anaemia. One is inclined to suggest, therefore, that the supplementing action of Jacobson and SubbaRow's accessory factors may have been due to contamination with small proportions of their primary factor (presumably the anti-pernicious-anaemia factor in crude form); satisfactory responses might well have been obtained with larger doses of the primary factor alone.

No further significant advance was reported until 1945, when Emery and Hurran reported a concentrate fully active in a dose of 5.5 mg. In the following year Emery and Parker (1946) reported further concentration to a preparation active in a single dose of only 1 mg. These fractions were made by application of known techniques—in particular, repeated adsorption on charcoal, elution with phenol or with hot 65% alcohol, and salting-out with ammonium sulphate.

It is something of a tragedy to recall the considerable amount of analytical work that has been performed by some groups of investigators on material now known to have contained as little as 0.01% to 1% of the pure factor. It must be confessed that we fell into the same error ourselves in making preliminary chemical investigations on material containing only about 3% of the factor, under the impression that it must be approaching purity. It seemed appropriate at the time to carry out the various analyses, for there was no reason at all to anticipate the phenomenal potency of the crystalline factor. We now know that the human requirement is only about 0.001 mg. a day. The only substances known to be physiologically active in smaller amounts are such poisons as plutonium and botulinus toxin.

Partition Chromatography

Reviewing the situation in 1946 it seemed to us unlikely that any further advance would be made without the introduction of new techniques. There was also little doubt that the new approach required was some form of chromatography, preferably perhaps the recently introduced partition chromatography. This method employs a tube packed with an inert porous powder capable of soaking up a considerable proportion of water without appearing damp; the material to be separated is applied to this column dissolved in an organic solvent not completely miscible with water and development is continued with the same solvent. These columns do not differ in appearance from the familiar adsorption chromatograms using alumina, for example, but the mechanism of separation is different: it depends on differences in the partition of the various substances present between water (held in the pores of the solid) and the solvent, instead of upon differences in adsorbability. Such partition chromatograms, using damp silica and butanol, fulfilled our expectations. Liver extracts, sufficiently purified by the methods already outlined, separated readily into three coloured zones. Yellow material travelled quickly down the column; a pink zone travelled very much more slowly; a brown zone remained near the top of the column with a tendency to overlap somewhat into the pink zone. Nearly colourless material was also present between the pink and yellow zones.

It was an obvious step to use these colours as a guide in cutting up the chromatogram, but we were surprised to find it so effective, for nearly all the clinical activity was concentrated in the pink fraction. The same thing happened in other experiments. Nevertheless we expected that this would turn out to be merely an adventitious association of a red pigment with the active principle, and a faulty interpretation of some later experiments seemed to confirm this view. Already we had reached the stage of purification where a ton or so of liver was needed to provide a workable amount of material, and the lengthy procedures for preliminary concentration as well as inevitable delays in clinical testing made progress very slow.

About this time we received temporary discouragement from the announcements that folic acid was effective in pernicious anaemia, and that it could be made synthetically. It was soon clear, however, that our liver concentrates, though still impure, were weight for weight much more effective than folic acid. We were therefore dealing with a different substance, and its isolation was still of academic interest at least. Then, as the clinical shortcomings of folic acid gradually came to light, interest in the liver factor revived and indeed intensified.

The Active Red Factor

By now we were satisfied that colour and clinical activity were inseparable, but our pink material obstinately refused either to crystallize or to respond further to attempted purification by repeated partition or adsorption chromatography, fractional salting-out, or fractional precipitation by solvent mixtures. After a long period of frustration, further progress came suddenly from the observation that treatment with proteolytic enzymes like trypsin would break down persistent peptide impurities. On repurification by partition chromatography the product from the red band was eight times as intensely coloured as any previous fraction; it was later shown to be correspondingly more active clinically.

After a few more weeks spent in further purifying the minute amounts of red fractions remaining, we had the final satisfaction of watching the pure substance crystallize from aqueous acetone. But during those last weeks we were forestalled by the announcement that the Merck team under Karl Folkers had added one more vitamin to their conquests by isolating the same substance in crystalline form. Following proof of identity by exchange of

specimens (Lester Smith, 1949) we have now adopted the name vitamin B_{12} suggested by the American workers.

It is worth noting that the methods we have used for the isolation of the anti-pernicious-anaemia factor are almost exclusively physical rather than chemical (Fantes, Page, Parker, and Lester Smith, 1949). In other words, we have depended on such physical properties as solubility in salt solutions and solvent mixtures, adsorption on charcoal, alumina, and silica, and partition between water and solvents. The countercurrent principle, upon which both adsorption and partition chromatography depend, enabled us to exploit the small differences in such properties between the factor and associated impurities.

This has been necessary because the factor is singularly devoid of characteristic chemical properties. The only chemical precipitants that have been used with advantage are Reinecke acid and phosphotungstic acid, but these are not at all specific, as both will precipitate many basic compounds. Moreover, neither is essential to the isolation of the pure factor.

Here, then, is another reason why the pure factor could hardly have been isolated in earlier years before some of these physical methods were perfected.

Standardization of Dosage

One considerable advantage that will follow from this work is the ability to express the dosage of liver extracts and other concentrates of anti-pernicious-anaemia factor in accurate and logical terms. The microbiological assay method using crystalline vitamin B_{12} as a standard permits standardization in terms of vitamin B_{12} activity. There will no longer be any excuse for stating dosages as the number of millilitres of a liver extract or the milligrams of crude solids administered, or in "liver equivalents" or the weight of liver from which the dose is prepared. Clearly, all these are misleading on account of variations in the potency of the original liver, variable yields in the course of extraction and purification, and differences in the extent of purification as between one liver extract and another. On the other hand, the growing body of evidence that liver extracts owe their efficacy in macrocytic anaemias solely to their vitamin B_{12} activity, which can be accurately assessed microbiologically, puts this method of standardization on a very firm foundation.

Three Interesting Points

Interest did not slacken, even temporarily, with the isolation of crystalline vitamin B_{12}. For one thing, we were able to provide evidence (Lester Smith, 1948a), since reinforced (Cuthbertson and Lester Smith, 1949), for the existence of a second red factor, also clinically active in pernicious anaemia; indeed, it now appears probable that there are three such factors (Lester Smith and Cuthbertson, 1949). It is not known whether the others are more complex substances incorporating the molecule of vitamin B_{12} (analogous to the various conjugates of folic acid with glutamic acid) or whether they are chemical modifications of vitamin B_{12} (analogous to the various kinds of vitamin D or of penicillin).

The isolation of one of these factors in crystalline form has recently been announced from the Lederle Laboratories (Pierce *et al.*, 1949). It has been named vitamin B_{12b}, the name B_{12a} having already been used for an artificially produced hydrogenation product of vitamin B_{12}.

Secondly, the chemical nature of vitamin B_{12} is gradually being unfolded as supplies of this very scarce material become available. (See Lester Smith, 1948b; Rickes *et al.*, 1948b; Kaczka *et al.*, 1949; Brink *et al.*, 1949: Ellis *et al.*, 1949; and Brink and Folkers, 1949.) The most surprising discovery, announced almost simultaneously by the British and American teams, was the presence of an atom of cobalt in the molecule—the first time this metal has been found in a pure substance of biological origin. This has given rise to a crop of speculations on the function of cobalt in nutrition, and the relation (if any) between vitamin B_{12} and the already known need of ruminants for cobalt. The molecule of vitamin B_{12} contains some readily hydrolysable group essential to its microbiological activity, since it is slowly inactivated by cold acid or alkali. This might be a phosphate ester group, although the phosphorus present is completely split off only on long heating with acid. This treatment also liberates a substance giving a positive ninhydrin reaction, but leaves the greater part of the molecule intact and still retaining the cobalt, though with altered solubilities. This has been disrupted only by fusion with alkali, when pyrrolic substances are released, suggesting some structural relationship with chlorophyll and haem pigments.

A third point of interest is a promising new source of vitamin B_{12}. This arose from an entirely different research on the "animal protein factor" required by chicks and some other animals reared on a vegetable-protein diet. It now appears likely that this factor is identical with vitamin B_{12}, but meanwhile it had been established that the factor is synthesized by some intestinal bacteria. This raised the possibility of production by a fermentation process, and the Merck group, doubtless turning first to fermentations already established, found that the factor is produced by *Streptomyces griseus* and succeeded in isolating crystalline vitamin B_{12} from the metabolism fluid of this organism (Rickes *et al.*, 1948c). Whilst the isolation of the crystalline product remains at present a complex and expensive procedure, the industrial production in this country of a purified vitamin B_{12} concentrate from fermentation liquors is now at an advanced stage. It is expected to become generally available shortly.

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VITAMIN B_{12} IN PERNICIOUS ANAEMIA: PARENTERAL ADMINISTRATION

BY

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The isolation of a red crystalline anti-pernicious-anaemia factor from liver was achieved almost simultaneously by Rickes, Brink, Koniuszy, Wood, and Folkers (1948) in America, and by Lester Smith and Parker (1948) in Great Britain. American workers were aided greatly by microbiological assays (Shorb, 1948), whereas in Britain attention was concentrated on testing each fraction in patients with pernicious anaemia in relapse. The 84 clinical tests begun in 1946* which guided Lester Smith's purification to the final stage of crystallization are of little medical interest and will not be described.

This report concerns only the pure crystalline material isolated by Lester Smith in Glaxo Laboratories, Greenford, which has proved to be identical with vitamin B_{12}. Chemical and physical properties are reported elsewhere by Lester Smith (1948), and by Fantes, Page, Parker, and Lester Smith (in the press).

Material and Methods

The 53 cases selected had the usual diagnostic features of pernicious anaemia, including megaloblastic marrow and histamine-fast achlorhydria. A few patients had relapsed after stopping treatment, but most had never been treated.

To limit the intake of extraneous haematopoietic factors during the initial test periods, meat, poultry, offal, meat products, yeast products such as "marmite," eggs, fresh fruit, and vitamin preparations were excluded from the diet, which contained white or National flour, processed cereals, sugar, jam or syrup, dried fruit, vegetables, butter and other fats, white fish, cheese, and 1 pint (570 ml.) of milk daily.

Reticulocytes were counted daily by a wet method using brilliant cresyl blue. Haemoglobin was determined by the cyan-haematin method of King and Gilchrist (1947). Red blood cells were counted every five days with N.P.L.-tested pipettes on a Bürker haemocytometer. Blood was diluted 1 in 200 with Hayem's fluid and at least six areas 1 by 0.05 mm. were counted. A test designed to measure the accuracy of counts by taking morning and afternoon specimens in 10 patients with anaemia showed that the standard error was ±6%.

For a control period of 7 to 10 days treatment was withheld so that patients showing signs of spontaneous remission could be excluded. A shorter control period was permitted if anaemia increased rapidly. A few cases were rejected because of intercurrent illness and one because of hypoplasia of the marrow. Also excluded were results rendered invalid by deterioration of vitamin B_{12} in very dilute solution (1 μg. per ml.)—a difficulty which has since been overcome.

Vitamin B_{12} was given intramuscularly as a single dose. Doses were graded logarithmically from 1.25 to 160 μg. An extra group was given 6.5 or 7.5 μg. (mean 7.2) because a level of dosage between 5 and 10 μg. was then believed to be critical (see later).

Patients with red blood cell counts above and below the mean level of 2,000,000 per c.mm. were, so far as possible, distributed equally in the groups receiving low, medium, and high doses.

Results

There were no unpleasant side effects, and sensitization to vitamin B_{12} was not encountered. The magnitude of the haematopoietic response was gauged partly from the reticulocyte crisis, but mainly from the rate of increase of red blood cells. A summary of 73 responses in 53 patients is given in Table I. An example is shown in Fig. 1.

TABLE I.—*List of All Responses*

	Dosage in μg.	Reticulocyte Response (%)	Red Blood Cell Counts (Millions per c.mm.) at Days Indicated						
			0	5	10	15	20	25	30
1	1·25	5·2	1·33	1·46	**1·60**	1·26			
2	,,	Nil	2·23	2·12	2·27	2·36	2·58	**2·62**	2·54
3	,,	Nil	**2·61**	2·56	2·49	2·45			
4	2·5	11·0	1·17	1·24	**1·46**	1·32			
5	,,	9·2	1·20	1·31	**1·59**	1·49	1·31		
6	,,	12·2	1·68	1·68	2·20	**2·25**	2·21		
7	,,	13·0	1·74	1·98	2·40	2·39	**2·43**	2·06	
8	,,	7·6	1·74	1·69	**1·95**	1·73	1·68		
9	,,	12·6	2·65	2·77	3·07	3·05	3·35	**3·62**	
10	5·0	P.T.	1·23	1·02	1·85	**2·18**	1·86		
11	,,	12·2	1·49	1·69	2·56	**2·62**	2·54		
12	,,	12·6	1·56	1·58	**2·58**	1·89			
13	,,	P.T.	1·57	1·93	2·30	2·80	3·12	**3·36**	
14	,,	10·2	1·88	1·84	2·93	**4·02***	3·87		
15	,,	7·6	3·00	3·17	**3·76**	3·75	3·70		
16	6·5 or 7·5	17·8	1·21	1·52	1·93	**2·28**	2·28		
17	,,	29·2	1·31	1·37	**2·77**	2·71			
18	,,	P.T.	1·33	1·58	**2·58**	2·52			
19	,,	25·0	1·77	1·66	2·98	3·40	**3·41**		
20	,,	19·6	1·77	1·99	2·31	2·59	**2·99**		
21	,,	P.I. (12)	1·89	2·04	**2·46**	2·26			
22	,,	25·8	1·96	1·77	**2·79**	2·44			
23	,,	10·6	2·02	2·26	2·68	**3·84**	3·42		
24	,,	9·2	2·07	2·15	2·63	**3·01**	2·82		
25	,,	P.I. (34)	2·24	2·58	3·47	3·82	**4·17**		
26	,,	6·8	2·24	2·35	**3·35**	3·04			
27	,,	3·8	2·33	2·44	2·71	3·22	3·00		
28	,,	P.I. (17)	2·71	2·93	3·69	**3·92**	3·51		
29	,,	P.I. (27)	3·00	3·19	**3·60**	3·32	—		
30	10·0	P.T.	1·10	1·57	2·60	**2·86**	2·80		
31	,,	P.T.	1·34	1·46	**2·08**	2·06	—		
32	,,	30·6	1·40	1·62	2·68	**3·16**	3·00		
33	,,	38·6	1·43	1·80	2·78	2·98	**3·05**		
34	,,	P.I.	1·45	1·83	**2·59**	2·24			
35	,,	P.I. (31)	2·10	2·26	2·76	**2·82**			
36	,,	P.I. (21)	2·26	2·31	2·96	3·08	**3·63**	3·26	
37	,,	P.I. (22)	2·44	2·62	3·60	**3·69**	3·63		
38	,,	P.I.	2·54	2·32	**3·80**	3·75			
39	,,	P.I. (11)	2·54	2·73	3·09	**3·12**	3·01		
40	,,	P.I. (32)	3·00	3·18	**3·75**	**4·12**	4·01		
41	,,	P.I. (26)	3·04	3·23	**4·16**	4·13	3·96		
42	,,	P.I. (44)	3·05	3·24	4·10	**4·37**			
43	,,	P.I.	3·05	3·23	4·01	4·22	**4·56**	4·04	
44	20·0	41·8	0·97	1·26	2·26	2·66	2·96	**3·17**	3·15
45	,,	27·6	1·26	1·50	2·28	2·39	**2·51**		
46	,,	>15	1·46	1·55	2·49	3·26	3·50	**3·61**	3·45
47	,,	34·0	1·62	1·64	2·55	**2·65**	2·59		
48	,,	28·0	1·76	1·91	2·86	3·27	**3·53**	3·39	
49	,,	18·4	2·28	2·45	3·49	3·55	3·87	**4·19**	4·09
50	,,	P.I. (47)	2·59	2·73	3·19	**3·59**	3·51		
51	,,	P.I. (39)	3·01	3·38	3·71	3·76	**3·81**		
52	40·0	P.T.	0·98	1·45	2·44	2·78	—	**3·53**	3·45
53	,,	22·8	1·35	1·44	2·83	**2·96**	2·66		
54	,,	P.T.	1·45	1·40	2·53	3·17	3·21	3·33 (4·54 at 49 days)	3·72
55	,,	38·0	1·77	2·14	3·09	3·28	**3·63**	3·64	
56	,,	P.T.	2·02	2·31	3·18	3·57	3·73	**3·90**	3·74
57	,,	7·2	2·06	2·45	3·09	3·46	—	—	4·11
58	,,	5·2	2·19	2·38	2·90	**3·44**	2·86		
59	,,	P.I.	2·28	2·53	3·08	3·67	**4·32**		
60	,,	P.I. (53)	2·66	2·90	**4·41**	4·30			
61	,,	3·4	3·03	3·18	**4·51**	4·45			
62	80·0	P.I. (1)	1·22	1·90	3·03	3·46	3·51	**3·57**	
63	,,	P.I. (5)	1·31	1·99	2·76	3·00	3·17	**3·53**	3·23
64	,,	P.T.	1·32	1·79	3·23	3·66	4·22	**4·30**	4·22
65	,,	26·2	1·59	1·93	2·79	3·66	3·98	**4·06**	
66	,,	P.I. (8)	1·68	2·11	3·04	3·19	**4·25**	4·10	
67	,,	26·4	1·70	1·81	2·82	3·27	3·41	**4·27**	4·16
68	,,	P.I. (7)	2·06	3·41	3·52	**3·87**	3·33		
69	,,	P.I. (6)	2·13	2·31	3·12	4·14	4·11	4·20	**4·82**
70	,,	P.I. (3)	2·45	2·61	3·76	4·16	3·91	4·06	**4·82**
71	,,	16·2	2·66	3·03	3·34	**4·17**	—		
72	160·0	19·4	1·27	1·50	2·32	3·42	**3·45**	3·29	
73	,,	21·0	1·71	2·02	3·17	3·72	**3·79**	3·70	

The highest count is in black figures. In a few instances counts recorded at 20 to 30 days were made a day or so before or after the time indicated. P.T. = previous transfusion. P.I. = previous injection; a number in brackets indicates the previous response; where no number appears the previous injection was of material not referred to in this paper (see under "Increase of Red Blood Cells" below.

* This freak response is excluded from calculations for Figs. 4 and 5 and Tables II and IV.

*In the early stages of this investigation some additional tests were carried out in Stobhill Hospital, Glasgow, by Dr. J. R. Lauckner, whose co-operation is gratefully acknowledged.

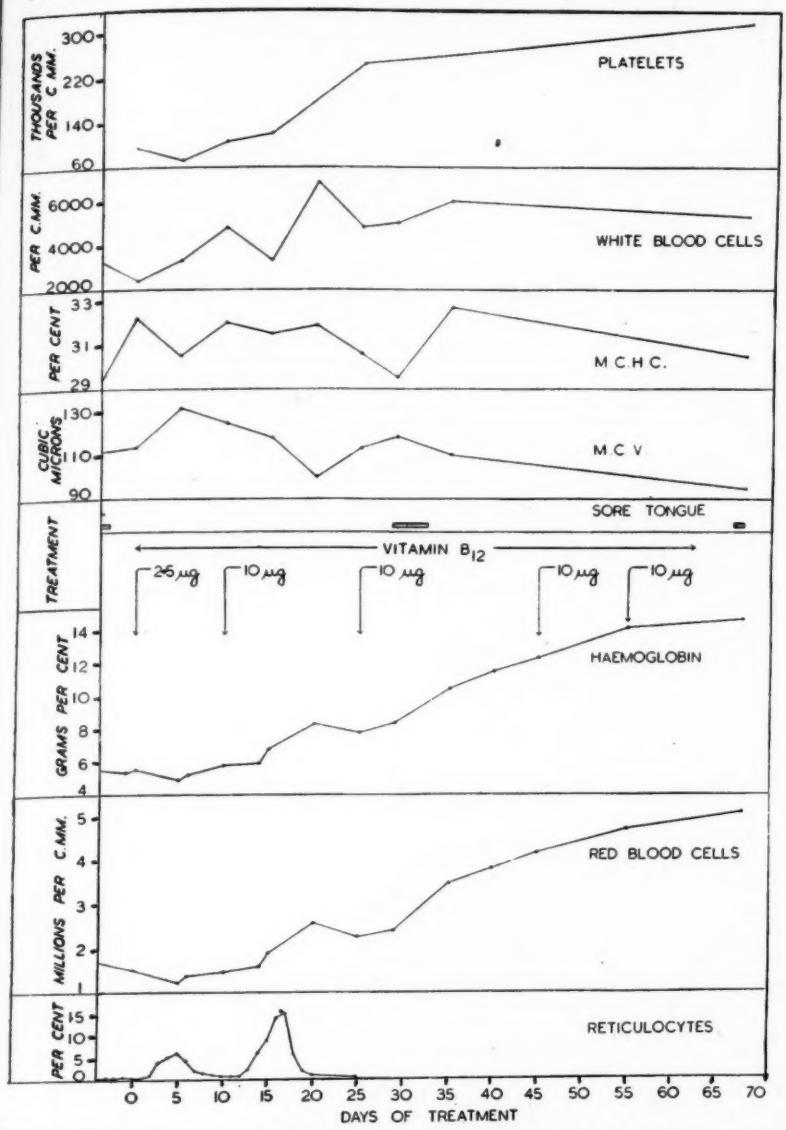

FIG. 1.—Response to repeated injections of Vitamin B_{12} in a patient with pernicious anaemia.

Reticulocytes

Reticulocytes usually began to rise on the second or third day, reaching a peak on the fifth or sixth day (counting the day of treatment as 0). There was a definite association between high dosage and early reticulocyte peak. With large doses—20 to 160 µg.—the peak usually occurred on the fifth day; with doses below 10 µg. the peak was usually on the sixth or occasionally the seventh day.

Reticulocyte responses of 39 patients, none of whom had had previous transfusion or injection, were compared with an "expected" response based on results to liver extract given intramuscularly (Isaacs and Friedman, 1938). Fig. 2 shows the actual responses at each initial red blood cell count. In Fig. 3 results are expressed as percentages of the expected response. Individuals varied widely in their response to a given dose. In more than 50% (10 out of 17) of the patients who received doses of 10 µg. and upwards the expected response was exceeded, whereas with smaller doses (1.25–7 µg.) this response was seldom attained (four times in 22 patients). A high reticulocytosis was not always the precursor of a satisfactory rise of red blood cells, confirming previous criticisms of the reticulocyte response as a measure of potency (Murphy, 1933; Ungley, 1936; Della Vida and Dyke, 1942; Fullerton, 1945).

Increase of Red Blood Cells

A better yardstick was the rate of increase of red blood cells. This depended not only on the dose of vitamin B_{12} but also on the initial count, and these factors varied independently of one another. Thus a formula became necessary to judge whether rates of increase were satisfactory or not.

For its construction we needed more data than were provided by the first responses in the 40 patients who had had no previous treatment. We had to decide whether to include certain additional data—namely, nine responses in patients who had been transfused with a small number of red blood cells, the survival of which could be followed by differential agglutination (Dr. Walker), and 24 responses in patients who had previously received small amounts of vitamin B_{12} (20 of them in the course of this trial). Such responses were not included unless there had been a satisfactory control period of seven to ten days of stationary or falling counts, as described under "Material and Methods" above. Where doubt existed a marrow puncture was performed and a further injection was given only if the marrow was megaloblastic.

In the nine transfused cases the average increase in the patient's own red blood cells in 15 days was 1,470,000, compared with an "expected" average increase of 1,400,000 calculated by the formula given below.

In the 24 patients who had relapsed after small amounts of vitamin B_{12} the average increase of red blood cells in 15 days was 1,220,000, whereas the expected average was 1,250,000.

In the 33 cases in these two groups the actual average increase was 1,290,000 compared with an "expected" increase of 1,290,000. Although, as described below, the "expected" increase has been calculated from a group of 63 patients which includes these 33, it is apparent from the above averages that the 30 patients who did not receive any previous treatment could not have differed significantly from the 33 patients who had had previous treatment. It was therefore considered justifiable to include the latter in the trial and to deal with them as normal cases. They are identified in Table I by P.I. (Previous Injection) and P.T. (Previous Transfusion). This neither assumes nor proves that such past treatment never has a serious effect on the rate of increase of red blood cells, but implies that such effects, if present, could be ignored in this series.

In all there were 73 satisfactory tests in 53 patients available for analysis.

Increase of Red Blood Cells in 15 Days

Increase of red blood cells in 15 days was the most useful criterion of response. Della Vida and Dyke (1942) have shown that the average weekly increase over the first two weeks of treatment depends on the initial level and varies inversely with it. Thus patients with fewer red blood cells at the beginning of treatment respond more rapidly than those who have higher counts, and conversely.

For each group of patients receiving similar doses a line was calculated by methods comparable to those of Della Vida and Dyke, and in every case, except for those receiving 2.5 µg., there was a marked relationship between the 15th-day increase and the initial count. But individually

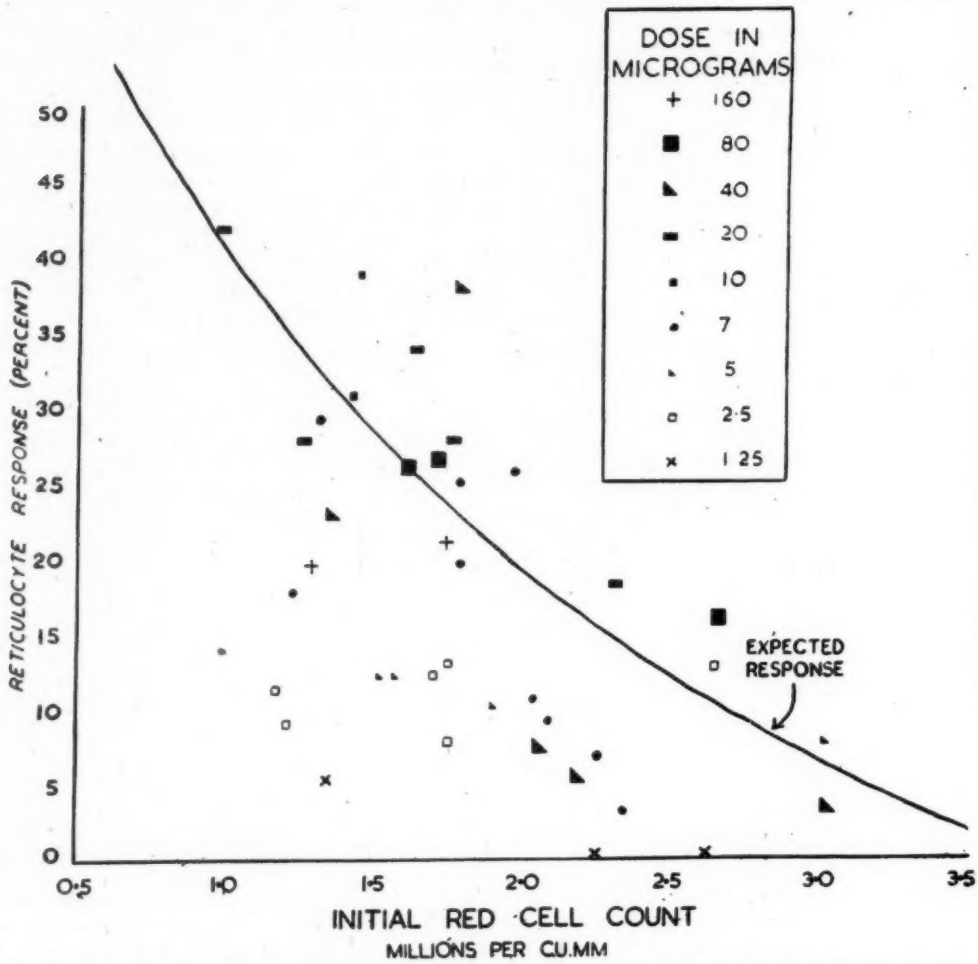

FIG. 2.—Reticulocyte responses (peak) in 39 patients to their first injection of vitamin B_{12} compared with expected response to liver extract calculated from formula of Isaacs and Friedman (1938).

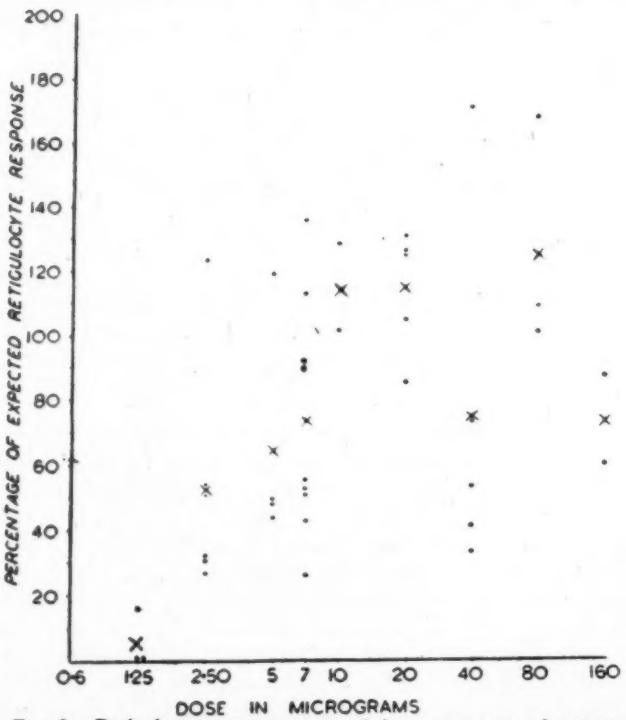

FIG. 3.—Reticulocyte response expressed as percentage of expected response. Crosses indicate the mean response at each level of dosage. Doses are spaced logarithmically.

none of these relationships could be considered statistically significant, because of the few cases involved, the largest group being 14. It was therefore necessary to calculate a formula making allowances for the differences in dosage and differences in initial blood counts at the same time.

The problem was simplified when it became apparent that over a certain range of dosage (5–160 μg.) the response varied according to the logarithm of the dose. (In practice this means that doubling the dose produces a constant increase in response.)

Out of 64 cases* receiving 5–160 μg. 63 were therefore used to calculate the formula by methods of multiple correlation, giving the following results:

$$I_{12} = 1.008 - 0.153\ E + 0.245\ D - 0.017\ E \times D.$$

Where I_{12} = Increase in red blood cells (millions per c.mm.) on the 15th day.

E = Initial red blood cell count (millions per c.mm.) on the day of injection.

D = Dose on a logarithmic scale—e.g. (5 μg. = 1; 10 μg. = 2; 20 μg. = 3; 40 μg. = 4).

The increases that may be expected according to this formula are given in Table II, and the lines have been superimposed upon Fig. 4.

This formula is applicable only for doses between 5 and 80 μg.—or possibly 160 μg.—and for patients whose initial

TABLE II.—*Expected Increase in 15 Days*

$I_{12} = 1.008 - 0.153\ E + 0.245\ D - 0.017\ E \times D$

Standard Deviation of $I_{12} = 0.33$

Initial Red Blood Cell Count (Millions)	5 μg.	10 μg.	20 μg.	40 μg.	80 μg.
1·00	1·08	1·31	1·54	1·77	2·00
1·10	1·07	1·29	1·52	1·75	1·97
1·20	1·05	1·27	1·50	1·73	1·95
1·30	1·03	1·25	1·48	1·70	1·92
1·40	1·01	1·23	1·46	1·68	1·90
1·50	1·00	1·21	1·44	1·66	1·87
1·60	0·98	1·19	1·42	1·64	1·85
1·70	0·96	1·18	1·40	1·61	1·83
1·80	0·94	1·16	1·38	1·59	1·80
1·90	0·93	1·14	1·36	1·57	1·78
2·00	0·91	1·12	1·34	1·55	1·76
2·10	0·89	1·10	1·32	1·53	1·73
2·20	0·88	1·08	1·30	1·51	1·71
2·30	0·86	1·06	1·28	1·48	1·68
2·40	0·84	1·04	1·26	1·46	1·66
2·50	0·82	1·02	1·24	1·44	1·64
2·60	0·81	1·01	1·22	1·42	1·61
2·70	0·79	0·99	1·19	1·39	1·59
2·80	0·77	0·97	1·17	1·37	1·57
2·90	0·75	0·95	1·15	1·35	1·54
3·00	0·74	0·94	1·13	1·32	1·52
3·10	0·72	0·92	1·11	1·31	1·50

E = Initial red blood cell count in millions. I_{12} = Increase in red blood cells on the 15th day. D = Dose on a logarithmic scale (5 = 1; 10 = 2; 20 = 3; 40 = 4; 80 = 5).

The error made in using these tables will be less than the Standard Deviation in about 68% of all individual cases.

*Case 14 was excluded, as the response was most exceptional.

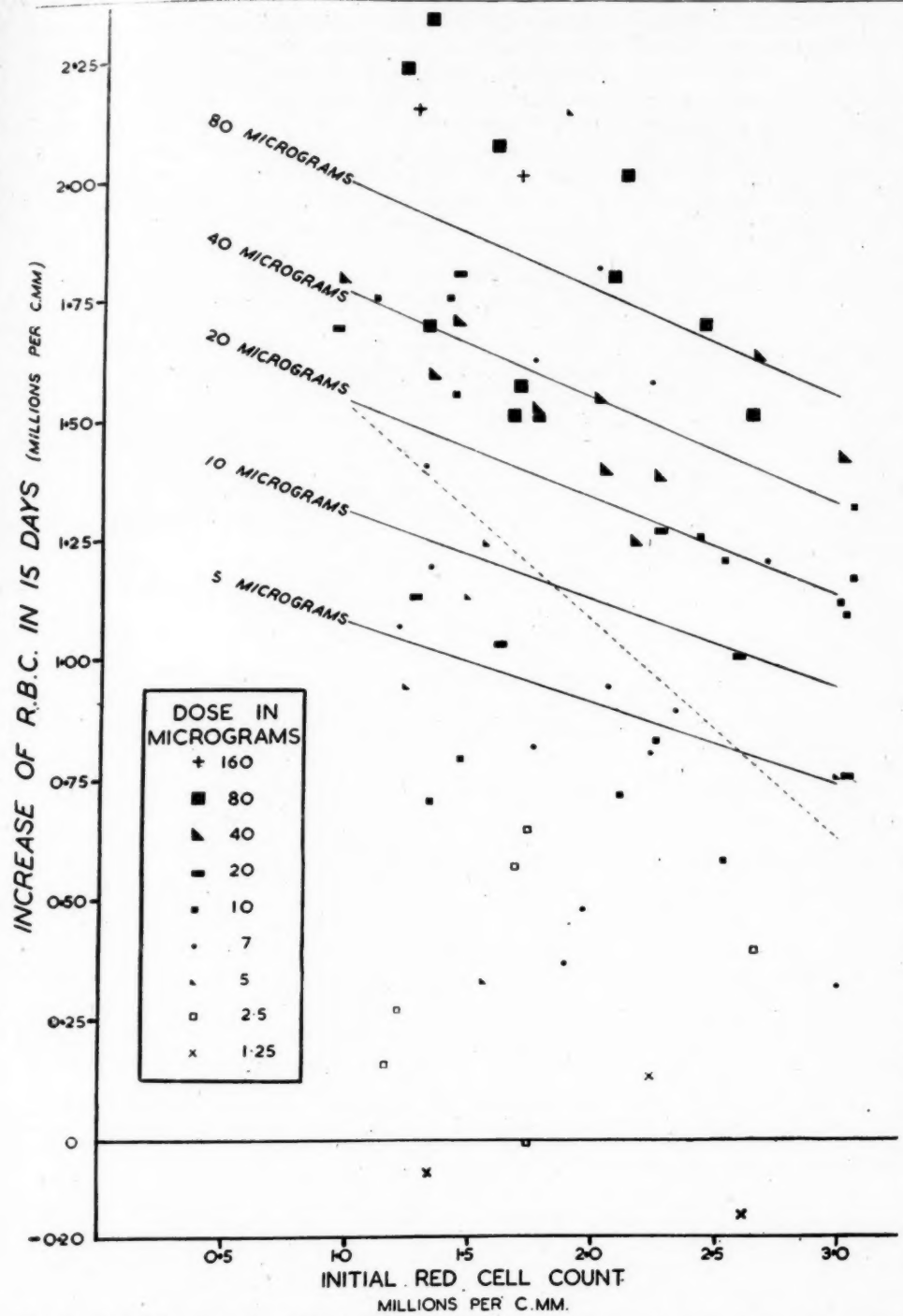

FIG. 4.—Actual increase of red blood cells in 15 days in 73 instances after vitamin B_{12}. The lines are calculated from a formula which takes account of dosage and initial red blood cell count. The dotted line corresponds to the formula of Della Vida and Dyke (1942) for "average" responses to liver extract.

red blood cell count lies between one and three millions per c.mm. Patients vary considerably in their response to treatment, but only 32% of responses will differ from the figures given in Table II by more than ±330,000. For groups of patients, however, the *average* increase of a group will be more accurate (e.g., for a group of 10 cases the average increase will usually be forecast by Table II with an accuracy of ±100,000).

The following is a brief explanation of the meaning of the formula, simplified by omitting the slight correction for the factor E×D. If a patient has an initial red blood cell count of 2,000,000 and is given an injection of 10 μg., the increase in 15 days will be about 1,120,000, making his actual count on the 15th day 3,120,000. For every doubling of the dose in the range 5 to 80 μg. there will be an additional increase of about 220,000, so that the increase in 15 days if the patient had received 20 μg. would be 1,340,000, and if 40 μg., 1,560,000. Similarly, for every million cells above 2,000,000 at the initial count the 15-day increase will be reduced by about 200,000, so that the increase for a patient with an initial count of 3,000,000 receiving 10 μg. is about 920,000. Similarly, for every million cells below 2,000,000 there will be an additional increase of about 200,000, so for a patient with an initial count of 1,000,000 the increase would be about 1,320,000 per c.mm.

The expected response found by Della Vida and Dyke for their "average" group was attained in our series by doses in the region of 10 μg., and only in this limited sense can amounts of this order be regarded as the "minimal effective dose" (Ungley, 1948b).

To check the validity of the formula the expected increases in 15 days were calculated for all 63 patients and compared with the actual increases obtained. The differences between these figures are given in Table III, where it will be noted that in over three-quarters of all the cases the error was less than 400,000. (The standard deviation of this table is ±320,000, which corresponds with that quoted in Table II.)

Dosage Response Curve Based on Increase of Red Blood Cells in 15 Days

The basic assumption made in calculating the formula was that the mean response to a given dose was proportional

TABLE III.—*Differences Between Estimated and Observed Increase of Red Blood Cells in 15 Days*

Estimate	Difference in Million R.B.C.	Cases
Too small	0·60–0·79	2
	0·40–0·59	4
	0·20–0·39	12
	0·01–0·19	13
Accurate	0	2
Too large	0·01–0·19	12
	0·20–0·39	11
	0·40–0·59	5
	0·60–0·79	2
		63

to the logarithm of the dose. While this is a justifiable assumption over a given range, it is unlikely to be true over the total range of possible doses.

It was therefore necessary to examine the assumption more closely to see if it was justifiable and at what stage it broke down. Accordingly, the difference between actual and expected increases was calculated for each case; for doses outside the range of Table II the formula was extrapolated. The mean difference for each dose group is given in Table IV and Fig. 5.

TABLE IV.—*The Mean Difference Between Observed and Expected Increase in 15 Days*

Dose in μg.	No. of Cases	Mean Initial R.B.C. (Millions per c.mm.)	Mean Difference (Millions per c.mm.)
1·25	3	2·06	−0·52
2·5	6	1·70	−0·40
5·0	5*	1·77	−0·07
7·0	14	1·99	+0·02
10·0	14	2·20	+0·05
20·0	8	1·87	−0·10
40·0	10	1·98	−0·02
80·0	10	1·81	+0·05
160·0	2	1·49	−0·02

*i.e., excluding Case 14.

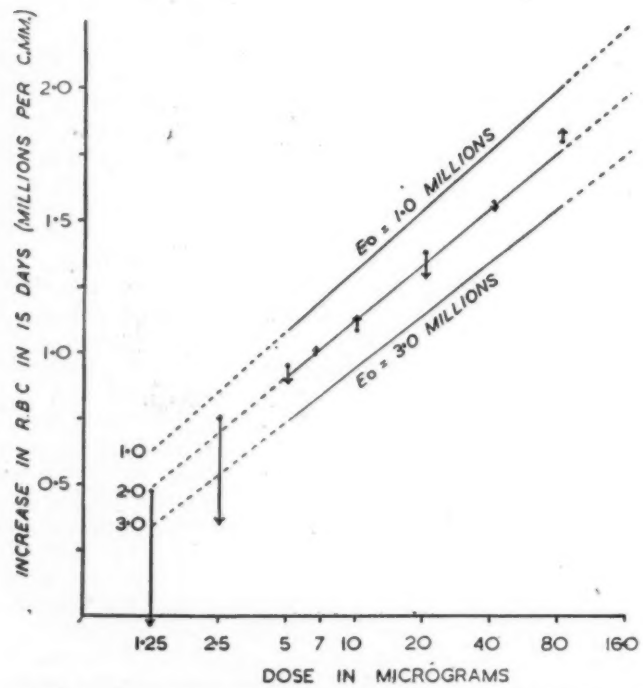

FIG. 5.—Dose response curve to graded doses of vitamin B_{12} (spaced logarithmically). Continuous lines = expected response according to formula in text. Difference between observed means and expected increase is shown by vertical lines. Dot = initial count; length of line = deviation from expected response; arrow shows whether deviation was above or below expectation. The relationship between response and log. dose did not hold for doses below 5 μg.

From Table IV it is apparent that doses below 5 μg. failed to produce a response proportional to the logarithm of the amount used. But for doses from 5 μg. to 160 μg. there is no significant departure from the logarithmic curve. Consequently, with the data available it may be concluded that between the stated limits the logarithmic is the most satisfactory approximation to the true dose response curve.

Below the stated limits a dose of 2.5 μg. produced fair reticulocytosis but a slow increase of red blood cells which was poorly sustained. The smallest amount given so far has been 1.25 μg., which produced slight reticulocytosis in one out of three cases with little or no increase in red blood cells in 15 days. Further tests are necessary to complete the curve and examine its behaviour for dosage levels at and above 160 μg.

An incidental finding is the considerable variation of the response, which is greater with small than with large doses (see Table VII). Variation in response might be due to a number of causes. Errors due to deterioration of vitamin B_{12} in solution and inaccuracy in measurement of dosage are believed to be small. Variation in the rate of absorption from the site of injection is probably significant only in so far as it affects the rate of excretion of vitamin B_{12} in the urine, itself probably an important factor. Individual requirements probably vary with such factors as age, sex, body weight, pyrexia, and metabolic rate. Another possible source of error is variable ingestion, utilization, and reserves of accessory haematopoietic factors, such as folic acid, which are present even in the restricted diet. The smaller variation in response after large doses suggests that they neutralize some of the sources of variability.

Increase at 5, 10, and 20 Days

Although the increase in 15 days was the most useful criterion for judging the potency of vitamin B_{12}, counts were also available for the 5th, 10th, and 20th days.

The increase in 5 days was slight—usually about 15% of the increase at 15 days (Tables V and VI). But precisely

TABLE V.—*Mean Red Blood Cell Counts During First 20 Days of Treatment*

Dose in μg.	No. of Cases	Mean Red Blood Cell Count at				Cases Followed 20 Days		
		0 Day	5 Days	10 Days	15 Days	No.	R.B.C. 0 Day	R.B.C. 20 Days
1·25	3	2·06	2·05	2·12	2·02	1	2·23	2·58
2·5	6	1·70	1·78	2·11	2·04	5	1·80	2·20
5·0	6	1·79	1·87	2·66	2·88	5	1·83	3·02
7·0	14	1·99	2·13	2·85	3·03	8	2·02	3·02
10·0	14	2·20	2·39	3·21	3·33	9	2·25	3·52
20·0	8	1·87	2·05	2·85	3·14	8	1·87	3·28
40·0	10	1·98	2·22	3·21	3·51	6	1·84	3·44
80·0	10	1·81	2·29	3·14	3·66	9	1·72	3·78
160·0	2	1·49	1·76	2·75	3·57	2	1·49	3·62

TABLE VI.—*Increases as a Percentage of that Reached in 15 Days*

Dose in μg.	5 Days	10 Days	15 Days	20 Days
5	7	80	100	109
7	13	83	100	114
10	17	90	100	113
20	14	77	100	112
40	16	80	100	105
80	25	72	100	111
160	13	60	100	103
All ..	17	81	100	110

the same characteristic variations were discernible, the increase varying with the logarithm of the dose and inversely with the initial count. The greatest rise was between the 5th and 10th days, by which time about 80% of the increase obtained in 15 days had occurred. Again, the same variables operated and had to be sorted out by a formula similar to that given above for the 15th-day counts. As a measure of response the 10th-day counts would have been nearly as useful as the 15th-day counts, but the chance of error was less with the greater increase in 15 days.

The 20th-day counts unfortunately were not complete in all cases, as some 21 patients who had not responded

well to treatment needed further injection before reaching the 20th day and had to be withdrawn from the trial. The remainder are therefore not a representative group, but are biased by the survival of the fittest. In this group the average increase by the 20th day was about 110% of the increase in 16 days.

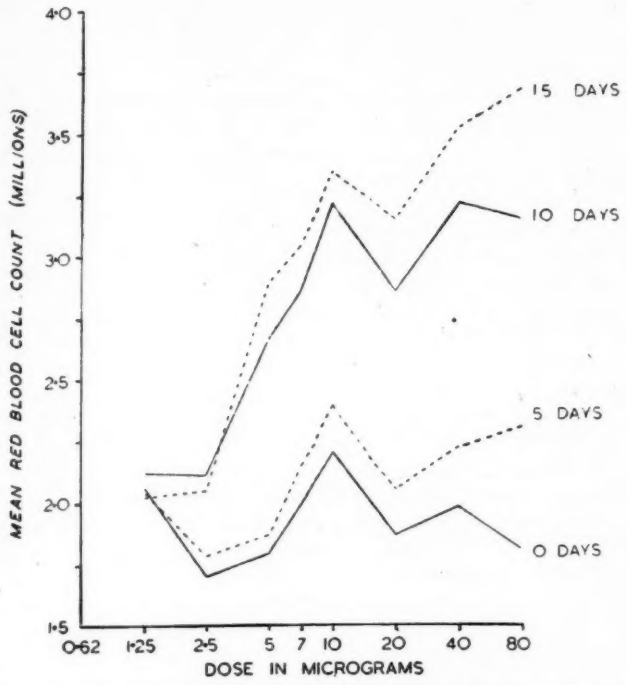

FIG. 6.—Mean red blood cell counts at fixed times after graded doses of vitamin B_{12} (spaced logarithmically).

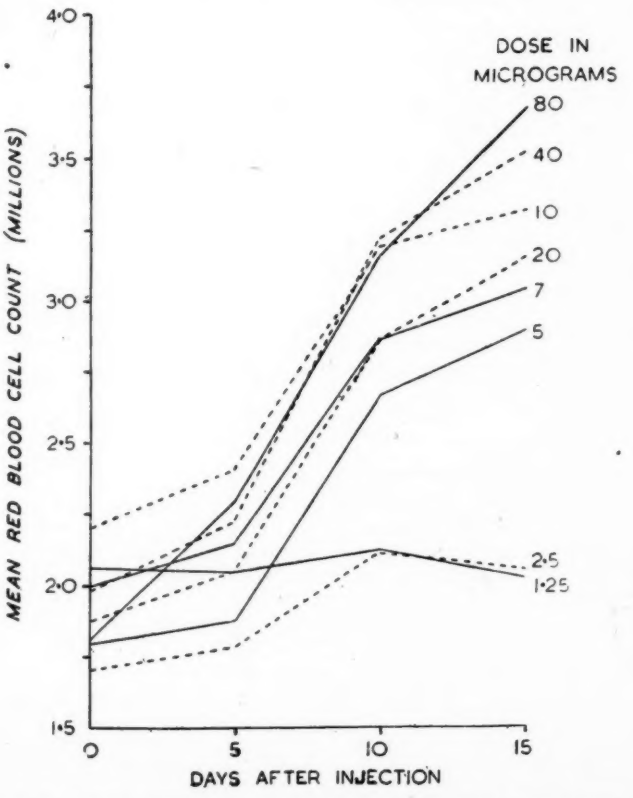

FIG. 7.—Mean response to graded doses of vitamin B_{12} (from same data as Fig. 6).

Fig. 6 shows the relationship between erythrocyte increase and dosage at various fixed intervals of time. In Fig. 7 the same data are arranged to show the behaviour of the erythrocyte counts over a period of 15 days for various fixed levels of dose. These figures show fairly clearly the relationship between time and dose and emphasize that higher doses produce responses which are not only greater but last longer. Fig. 8 shows the usual form of curve of increase of erythrocytes in the first three weeks after doses of 5–160 μg. (see Table VI).

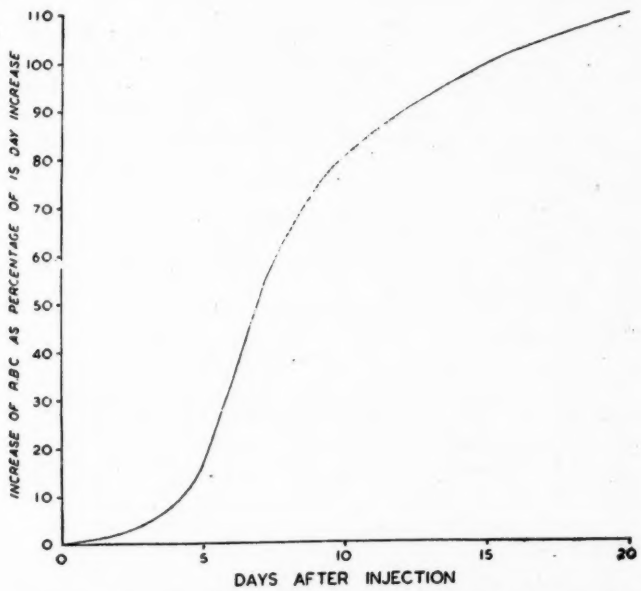

FIG. 8.—Proportion of increase of red blood cells which occurred in 5, 10, 15, and 20 days after a single dose of vitamin B_{12}. This form of curve holds true for most cases receiving doses of 5 to 160 μg. (see Table VI).

Total Dosage to Complete Remission

The amount of vitamin B_{12} required to raise the red blood cell count above 4,500,000 in 32 cases varied from 15 to 140 μg. and the time from 15 to 118 days. Individual findings are not recorded, since variations depended partly on the size and spacing of the doses. If red blood cell counts were allowed to fall before subsequent doses were given, then more time and material were required for complete remission. Moreover, remission was attained less economically with a single large dose than with the same amount of material given in divided doses at fortnightly intervals. Daily requirements for vitamin B_{12} could not be determined accurately from such data.

Other Findings

Changes in the *bone-marrow* from megaloblastic to normoblastic erythropoiesis after liver extract are described by Davidson, Davis, and Innes (1942) and after Lester Smith's non-crystalline red-pigmented material by Lorriman (1948). Similar changes following crystalline vitamin B_{12} were observed in the present series by Drs. G. Lorriman and R. B. Thompson (personal communication).

Initial *white blood cell counts* before treatment in 32 patients ranged from 1,500 to 8,300 (mean 4,300 ± S.E.260 per c.mm.). When remission was attained (red blood cells 4,500,000 per c.mm. or over) white blood cell counts in these patients ranged from 4,000 to 8,800 (mean 6,200 ±

170 per c.mm.). *Platelet counts*, too, usually rose to normal levels; Fig. 1 shows a typical response. Counts before treatment in 42 patients ranged from 20,000 to 283,000 (mean 105,500 ± 7,000). Counts 1 to 12 weeks later (mean 3.5 weeks) ranged from 120,000 to 560,000 (mean 305,500 ± 16,000). The difference between means both for white blood cells and for platelets is highly significant.

Within the first few days there was a dramatic increase in appetite and well-being, followed later by a gain in weight. Disturbances such as nausea, vomiting, and diarrhoea were relieved.

Soreness of the tongue usually disappeared within a few days, recurring only if the effects of an injection were allowed to wear off. Three exceptions are mentioned under "Maintenance." Clean smooth tongues became partially or completely repapillated and sometimes furred.

Neurological and certain other findings are discussed below.

Maintenance

Excluding cases with subacute combined degeneration, 21 patients were treated long enough (6 to 15 months) to give some indication of requirements for maintenance. The standard dose was 10 μg. every two weeks, although in two instances the interval was lengthened to three and four weeks, and in one the dose was increased because of sore tongue. To simplify further discussion the exceptions will be considered first.

Six women showed evidence of iron deficiency after 8 to 15 weeks, with low mean corpuscular haemoglobin concentration (M.C.H.C.); normality was restored by a course of ferrous sulphate.

Three of these women and one man mentioned below had isolated red blood cell counts of just below 4,000,000 per c.mm. in the maintenance period. In one of the women the low count followed an attack of influenza; the man had intermittently a sore tongue and some macrocytosis (mean M.C.V. 96.5 c.μ; range 90.4 to 101.6 c.μ), indicating that his requirements were not completely met by 10 μg. a fortnight.

Another patient complained of very slight soreness of the tongue at each attendance. A third had intermittently a red sore tongue, which was not relieved even when doses were stepped up to 80 μg. Neither of these two patients had abnormal blood findings during the maintenance period.

The mean values mentioned below were derived from the sum of all findings for each patient (including the exceptional cases) after red blood cells first reached 4,500,000 per c.mm.

Mean red blood cell counts ranged from 4,480,000 to 5,120,000 (mean 4,950,000). Mean haemoglobin values ranged from 11.1 to 14.7 g. (mean 13.8 g.) per 100 ml.

Except in the six women who developed iron deficiency, haemoglobin increased at a rate adequate to maintain a normal M.C.H.C. Mean values for M.C.H.C. for all cases ranged from 28.1 to 34.8% (mean 30.9%).

By the time the red blood cell counts had reached 4,500,000 the M.C.V. had usually fallen to normal (76 to 94 c.μ). Mean values during maintenance ranged from 81.1 to 96.5 c.μ (mean 89.6 c.μ). A few patients had isolated values of 96 to 99 c.μ, but only the one man already mentioned had any suggestion of persistent macrocytosis.

Findings in eight patients with subacute combined degeneration who received much larger doses of vitamin B_{12} (see below) are of interest. Mean red blood cell counts ranged from 4,850,000 to 5,550,000 per c.mm.; mean haemoglobin levels ranged from 13.8 to 15.4 g. per 100 ml. M.C.H.C. was always within the normal limits; so was M.C.V., apart from one isolated reading of 96.7 c.μ.

Neurological Manifestations

Twenty-one patients in this series have been followed for six to 15 months and others for shorter periods; neurological manifestations improved or remained unchanged and fresh symptoms have not developed.

More direct evidence of the efficacy of vitamin B_{12} against the neurological manifestations of pernicious anaemia was obtained by treating established cases of subacute combined degeneration (Ungley, 1948a, 1949). The first patient began treatment with Lester Smith's red but not yet crystalline material in December, 1947, changing to crystalline vitamin B_{12} six months later. Now eight patients have received pure vitamin B_{12}—usually 40 μg. a week—for a minimum of 10 months. Using a quantitative method of assessing neurological status, significant improvement was demonstrated in each case. Comparison with 44 patients treated before the war showed that vitamin B_{12} was as effective as liver extract—crude or refined—in the treatment of subacute combined degeneration (Ungley, 1949).

Routine dosage of vitamin B_{12} must cover wide individual variations in requirement and maintain reserves. Uncomplicated cases without neurological involvement may be given 40 to 80 μg. initially, followed by 20 μg. weekly for three months and 30 μg. every three weeks thereafter. Patients with subacute combined degeneration should receive weekly at least 40 μg. for six months and 20 μg. thereafter. Some will need more: at the least sign of relapse—lingual, haematological, or neurological—or if infection develops, dosage should be temporarily doubled or trebled.

Our findings amplify earlier reports on the effect of vitamin B_{12} given parenterally in pernicious anaemia (West, 1948; Ungley, 1948a, 1948b, 1949; Hall and Campbell, 1948; Spies, Stone, Kartus, and Aramburu, 1948; Berk, Denny-Brown, Finland, and Castle, 1948; Bethell, Meyers, and Neligh, 1948; Spies, Suarez, Garcia Lopez, Milanes, Stone, Lopez Toca, Aramburu, and Kartus, 1949; West and Reisner, 1949).

Subsequent papers will describe the effects of vitamin B_{12} administered via the alimentary tract; its effect in non-Addisonian megaloblastic anaemias; its effect in certain cases of megaloblastic anaemia showing rapid elimination of transfused red blood cells; and the effect in pernicious anaemia of factors related to vitamin B_{12}, including thymidine and Lester Smith's slow-moving red component.

Summary

Seventy-three responses to single doses of vitamin B_{12} injected intramuscularly were observed in 53 patients with pernicious anaemia in relapse.

Doses were graded logarithmically from 1.25 to 160 μg. Conclusions are based on the means of a number of responses at each dose level. Reticulocyte responses were compared with the "expected" response to liver extract according to Isaacs and Friedman (1938), but a better yardstick was the increase of red blood cells in 15 days.

While doses of 1.25 μg. had little or no effect, 2.5 μg. produced a definite but small response. Responses to 5 and 7 μg. were on average somewhat below, and to 10 μg. just up to expectation, both in respect to reticulocytes (Isaacs and Friedman, 1938) and to increase of red blood cells in 15 days (Della Vida and Dyke, 1942, formula for "average" group).

Only in this limited sense can 10 μg. be regarded as a minimal effective dose. Larger doses produced still greater increase of red blood cells in 15 days, the mean response being roughly proportional to the logarithm of the dose, at least in the range 5 to 80, or possibly even 160 μg. From a formula devised to express this relationship the expected response to any dose within the range was calculated. Most of the responses actually obtained did not differ from the expected response by more than 330,000 per c.mm.

Further tests at high and low levels of dosage are needed to complete the dose response curve, which will probably be sigmoid in form, rising gradually, then steeply, from the threshold dose, and flattening out to a horizontal level when supramaximal doses are reached.

Maintenance doses of 10 μg. of vitamin B_{12} every two weeks were satisfactory in 18 out of 21 patients followed for six to 15 months. The exceptions were three patients whose sore tongue was not completely relieved, one having macrocytosis in addition. Six women developed iron deficiency at eight to 15 weeks, relieved by ferrous sulphate.

Fresh neurological symptoms did not develop. Direct evidence of an effect in subacute combined degeneration is published elsewhere (Ungley, 1949).

I am indebted to medical, nursing, technical, and clerical members of the staff for their co-operation, and to general practitioners who referred untreated cases of megaloblastic anaemia: further progress in this field depends on their continued help. I am also indebted to Dr. E. Lester Smith and his colleagues in the Research Division of Glaxo Laboratories Ltd., Greenford, who prepared and supplied all the crystalline vitamin B_{12} used in these investigations.

APPENDIX

It was necessary to calculate from the data in Table I formulae which would give the number of red blood cells to be expected in a given patient after a given dose.

Regression lines were calculated between increase in red blood cells at 15 days (I_{15}) and the initial count (E) for each dose. These were as follows (Table VII):

Dose (μg.)	No. of Cases	Regression Line I_{15} in millions	Correlation	Std. Dev. of I_{15} in millions
2·5	6	$I_{15} = 0{\cdot}162 + 0{\cdot}101\ E$	+0·23	0.45
5·0	5	$I_{15} = 1{\cdot}039 - 0{\cdot}091\ E$	−0·18	0.50
7·2	14	$I_{15} = 1{\cdot}487 - 0{\cdot}226\ E$	−0·25	0.45
10·0	14	$I_{15} = 1{\cdot}432 - 0{\cdot}130\ E$	−0·26	0.34
20·0	8	$I_{15} = 1{\cdot}935 - 0{\cdot}339\ E$	−0·57	0.35
40·0	10	$I_{15} = 1{\cdot}824 - 0{\cdot}149\ E$	−0·55	0.14
80·0	10	$I_{15} = 2{\cdot}362 - 0{\cdot}285\ E$	−0·47	0.27

These lines indicate a consistent relationship between low initial red blood cells and high response at 15 days for all doses between 5 and 80 μg. There is, moreover, a suggestion that the dosage effect is on a logarithmic scale.

A fresh regression line was calculated for doses between 5 and 80 μg. for three variables I_{15}, E, and D, where D was the dose on a logarithmic scale—i.e., 5 μg.=1; 10 μg.=2; 20 μg.=3; 40 μg.=4; 80 μg.=5. (On this scale the intermediate dosage of 7.2 μg. corresponded to 1.5.) This gave formula 2:

$I_{15} = 1.168 - 0.199\ E + 0.193\ D$
Number of cases = 61
Corrected correlation between I_{15} and D = +0.60
" " " I_{15} and E = −0.31
Standard deviation of I_{15} = 0.33 millions

This formula, used for preparatory work on dosage response, compels the dosage lines to run parallel, whereas perhaps they should converge. To test this hypothesis another formula was calculated in which a fourth factor was introduced, $C = D \times E$. If there was a tendency for the lines to converge this would be apparent in the value of C. At this stage further data were available for two cases receiving 160 μg., and as these appeared to fall accurately on the extrapolation of formula 2 they were included in the calculation of formula 3, which was as follows:

$I_{15} = 1.008 - 0.153\ E + 0.245\ D - 0.017\ D \times E$
Number of cases = 63
Standard deviation of I_{15} = 0.33 millions.

This is the formula used in the text.

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The drawing up of a series of measures designed to strengthen health administrations in underdeveloped countries in the fight against tuberculosis is one of the main results achieved by the Expert Committee on Tuberculosis of the World Health Organization, which recently concluded a five-day session in Copenhagen. The importance of training health personnel in underdeveloped areas was stressed repeatedly by the experts. They pointed out that the World Health Organization could be of great assistance in setting up centres to train local personnel in all phases of tuberculosis control work and to serve as demonstration centres for medical and auxiliary personnel of the area. The committee further suggested that WHO might give useful information on certain types of hospitals which could be set up in a relatively rapid and economical way. Health education was recognized by the committee as an essential tool in tuberculosis control. It was urged that WHO should encourage national and international voluntary organizations to inform the public on all aspects of the tuberculosis programme carried out in a particular country with the purpose of securing active support for it. The value of tuberculin-testing and of B.C.G. vaccination as the only practical way known so far of producing specific resistance against tuberculosis was reaffirmed by the committee. Further, it was emphasized that B.C.G. immunization could be fully effective only if used as a part of a general programme in addition to the application of other available preventive measures. Mass vaccination with B.C.G. was specially recommended for countries with high tuberculosis infection and mortality rates. In connexion with the B.C.G. programme the committee heard a report on the work and plans of the research office which has been set up by WHO in Copenhagen to evaluate the results of tuberculin-testing and B.C.G. vaccination. The results to be expected from this WHO research group will be of great value to future planning of anti-tuberculosis campaigns on a world-wide basis.

VITAMIN E IN THE MENOPAUSE*

BY

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Menopausal flushing and sweating can usually be controlled by oestrogens, but the stimulating effect of these hormones on the genital tract and breasts sometimes contraindicates their use—for instance, after radium treatment of cancer or before cessation of menstruation. Although oestrogens promote cancer development in animals there is so far no proof that they do so in man (Gemmell and Jeffcoate, 1939; Gardner, 1947). Nevertheless, "cancer-like" areas are quite often a troublesome finding in curettings from patients whose oestrogen-withdrawal bleeding has necessitated curettage (Gusberg, 1947).

Vitamin E was first used by Evan Shute (1937) to control flushings, and several confirmatory reports have followed (Shute *et al.*, 1938; Hain and Sym, 1943; Christy, 1945; Ferguson, 1948; Finkler, 1949). In this study special attention has been paid to the genital tract to ascertain if vitamin E is inert and therefore a substitute for oestrogens or stilboestrol in cases in which stimulation of the genital tract is undesirable.

*Read before the Birmingham and Midland Obstetrical and Gynaecological Society on March 31.

The Investigation

Clinical Material.—In view of the cost (£7 per case), treatment was given only to patients seriously disabled by drenching sweats, flushings, loss of sleep, and so on. The incidence of severe flushing after cessation of menstruation is about 17%, while after radium or surgical castration the figure is 50% (McLaren, 1941). Vitamin E in the form of alpha-tocopherol ("ephynal") was given to 47 patients with severe flushings; these included four regarded as new cases, although in fact they had relapsed after successful treatment with vitamin E. Forty cases had not been previously treated, while three had resisted stilboestrol. The 47 cases fall into the following categories:

	Cases
Radium menopause (two years approximately)	25
Deep *x*-ray (one year approximately)	9
Hysterectomy and double oophorectomy	10
Hysterectomy and one ovary	2
Spontaneous menopause	1

As a control before vitamin E, 18 cases were treated as follows. After completion of her case history and pelvic examination the patient was given blank tablets and a card to record the number of flushes at each period of the day

TABLE I.—*Effect of Vitamin E on Flushing*

No. and Class	Vitamin E (mg.)	Days	Result	Blanks before Treatment		Blanks after Treatment		Spontaneous Relapse
				Days	Result	Days	Result	
778 Spont. M.	14,000	35	Fail					
732 *X*-ray	35,000	35	Part cure	12	Fail	28	Cure	Unknown
720 "	35,000	35	Fail	14	"			
701 Castrate	35,000	35	"	14	"			
722 *X*-ray	28,000	28	"	12	"			
725 "	54,600	21	Cure	10	"			Unknown (Case 3)
736 "	14,000	14	"	14	"	21	"	Cure (Case 4)
743 "	25,200	35	Fail	12	"			
730 "	35,000	35	Cure	14	"	49	Relapse	
745 "	21,000	21	"	19	"	28	Cure	Relapse 4/52
734 Castrate	35,000	35	"	14	"	35	Relapse	
739 *X*-ray	28,000	28	Part cure	24	"	35	Cure	Relapse 3/52
754 Castrate	28,000	21	" "	19	"	21	Relapse	
578 "	14,000	14	Cure	21	"	28	Cure	Relapse 4/52
466 Rad. M.	17,500	49	"					After oophorectomy relapse
573 1 ovary	30,700	65	"			14	"	Relapse 3/52
562 Rad. M.	12,600	26	Fail					
464 " "	8,300	35	Cure			106	"	Unknown
{450 " "	13,500	56	"			28	Relapse	
{585 " "	4,200	14	Fail					
452 " "	32,200	43	"					
615 Castrate	42,000	42	"					
668 Rad. M.	4,200	14	Cure	14	"	28	Cure	Cure 14/52
{561 " "	15,400	42	Part cure					Relapse 4/52
{561B " "	14,000	14	Fail					
293 Castrate	28,750	98	Cure			21	Relapse	
46 Rad. M.	5,110	42	"			63	Cure	Cure 10/12
112 " "	3,360	28	"				"	Unknown
{355 Castrate	5,600	14	"			21	"	Relapse 3/52
{355B "	10,000	21	"	42	"			Part relapse 4/52
263 Rad. M.	3,360	14	"			14	"	Relapse ?4/52
307 Castrate	18,060	56	Fail					
269 1 ovary	6,860	49	Part cure			21	Relapse	
106 Rad. M.	4,200	28	Fail					
108 " "	60,600	83	Cure	40	"	21	Cure	Relapse at once
176 " "	1,400	14	"					Unknown
324 " "	17,300	42	Fail					
451 " "	9,450	56	Part cure			14	"	Unknown
45 " "	8,400	63	Fail					
583 " "	12,600	21	Cure	21	Cure (40%)	28	Relapse	
172 " "	5,880	63	"			21	Cure	Cure 12/12
227 " "	1,680	14	Part cure					Relapse at once
514 " "	21,000	41	Fail					
47 " "	4,116	38	"					
149 " "	5,600	56	"					
225 " "	10,640	47	Cure					Relapse at once
157A Castrate	15,750	80	"			84	"	Cure 5/12
647 "	—	—	—	32	Cure	—	—	—

Spont. M. = Spontaneous menopause. *X*-ray = *X*-ray menopause. Castrate = Hysterectomy and bilateral salpingo-oophorectomy. 1 ovary = Hysterectomy and unilateral salpingo-oophorectomy. Rad. M. = Radium menopause. Part cure = Patient not completely relieved. Bracketed cases = Relapsed and retreated cases.

After intervals up to 42 days (average 19 days) only one case was cured (No. 647), while another was somewhat improved but was still in need of treatment.

The results of treatment of flushing by vitamin E are shown in Table I: 23 were completely cured, 7 were markedly improved, and 17 were failures. The dosage given was as follows: lowest, 1,400 mg.; highest, 60,000 mg.; average 18,500 mg.

Effect of Placebos.—Of 23 cured or improved cases, 22 were given placebos for periods varying from 14 to 106 days (average 35 days). Fifteen cases (68%) maintained their improvement, while seven relapsed. Flushing reappeared in four and partially reappeared in two cases, while 16 (73%) maintained the cure. Of 17 cases questioned up to a year after completion of treatment 12 had relapsed partially or completely, but five were completely free from symptoms. No information was available from the remaining six cases.

Analysis of Failures.—There was apparently no special "type" of menopause resistant to treatment—viz., radium menopause, 10 cases; hysterectomy and double oophorectomy, three cases; deep *x*-ray, three cases; spontaneous menopause, 1 case. In an attempt to overcome the resistance to treatment doses up to 60 g. (average 20.745 g.) were given over an average period of 36 days, but without success. The 17 "failures," however, were quickly cured of their flushings by small doses of stilboestrol.

Vitamin E and Sex Function

A recent survey of the effect of the radium menopause on sex function led to the belief that it speedily causes many patients to lose their normal libido and the ability to achieve the orgasm. Ten out of 100 cases, moreover, suffered from dyspareunia after radium (McLaren, 1949).

It was impossible to interview every patient, and often the information was quite obviously inaccurate—e.g., when the patient alleged satisfactory coitus yet on examination proved to have a painful lesion of the vulva or vagina. Accordingly only 22 out of 43 patients were considered to be giving reliable evidence, but from this number we concluded that vitamin E had little effect in restoring libido or on the achievement of orgasm. As will be described later, vitamin E has a slow effect in curing painful senile lesions in the genital tract, and to this extent it must contribute to improved sexual relations, although in this it does not compare with stilboestrol.

Effect of Vitamin E on the Genital Tract

The clinical material was drawn from patients who some two years previously had had the menopause induced by radium. Senile lesions in the genital tract are then quite common—e.g., bleeding spots were observed in the vagina on speculum examination in 11 out of 68 patients whose ages averaged 45, an incidence which would not be unusual in normal women 15 or 20 years later (McLaren, 1941, 1949). We therefore had the opportunity of testing the curative effect of massive doses of alpha-tocopherol on these and other senile genital lesions. Cell-smears were also studied to ascertain if the drug was in fact inert or caused any cell division or differentiation.

Shute *et al.* (1938) and Shute (1942) have reported healing in a proportion of cases of senile vulvo-vaginitis after vitamin E, while Rubenstein (1948) and Finkler (1949) both comment on the inert or poorly developed type of vaginal smear which follows vitamin E as compared with the high degree of maturation of cells which follows stilboestrol.

In 28 to 112 days slow but definite healing was observed in four senile vulvar lesions, while two cases were unchanged (Table II). Case 134 will be reported under "toxic reactions," for dermatitis compelled us to stop treatment. In this case we first noted a remarkable softening of the indurated vulva, then a diminution in pruritus, and, finally, almost complete healing, which was still maintained a year later.

TABLE II.—*Effect of Vitamin E on the Vulva and Introitus*

No. and Class	Disease	Dose (mg.)	Days	Result
45 Radium menopause	Red introitus bled easily	8,400	82	Very much improved
134 Carcinoma of body	Vulvitis, pruritus, excoriation	38,680	112	Almost cured, but skin reaction. (See below)
269 Hysterectomy and 1 ovary removed	Red tender introitus	6,860	28	No improvement
293 Hysterectomy and bilateral salpingo-oophorectomy	Patches of red (raw) areas at vulvo-vaginal junction	28,750	110	Cured
355 Radium menopause	Red introitus, tender caruncle	5,600	35	No improvement
263 " "	Introitus red, tender periurethral oedema	3,360	35	Healed

Effect of Vitamin E on the Vagina

In all, 30 cases were examined by a Cusco speculum before and after treatment. Twenty-two normal cases were unchanged, showing no undue vascularity or "blueing" such as one normally sees after stilboestrol. The remaining eight cases (Table III) had senile vaginitis; of these,

TABLE III.—*Effect of Vitamin E on Senile Vaginitis*

No. and Class	Disease	Dose (mg.)	Days	Result
269 Hysterectomy and 1 ovary removed	Senile vaginitis	6,861	49	No effect; bleeding spots persisted
*45 Radium menopause	Senile vaginitis (acutely) inflamed	8,400	82	Healed; no red or bleeding spots
615 Subtotal hysterectomy and two ovaries removed	Senile vaginitis	42,000	42	Cervix healed; little effect in vagina
*46 Radium menopause	Mild vaginitis	5,110	102	Improved, but still several bleeding spots
*106 " "	" "	4,200	56	No effect
*112 " "	" "	3,360	28	Healed
263 " "	" "	3,360	35	"
293 Hysterectomy and two ovaries removed	Red vagina (split and bled with small speculum)	28,750	112	"

* "Spots" also present on the portio cervicis.

two were apparently the result of a simple speculum examination using 30% "dettol" cream. After prolonged treatment with alpha-tocopherol four were cured and four were only slightly affected. It is possible, however, that simple hygienic measures with sexual abstinence would also have affected a cure.

As in the case of the vulva, therefore, vitamin E has a slow healing effect, but in no way compares with stilboestrol as a healing agent in senile vaginitis.

Effect of Vitamin E on Vaginal Smears

Certain types of vaginal smears are capable of giving a fairly accurate forecast of the state of development of the underlying mucosa—for instance, after stilboestrol therapy in a 70-year-old woman adult flat squamae replace small immature cells and leucocytes. It is necessary, however, to set a limit on what can be "read" from vaginal smears. For instance, in a previous report 138 biopsies and smears were correlated, but only adult smears and senile (small-cell) smears gave an accurate forecast of the epithelial maturity or senility. The remaining and most numerous smears with large squamae, spinosum cells, and small (immature) cells could not be "read" with accuracy (McLaren, 1941). With these limitations in mind, and aware that only gross changes such as "stilboestrol effects" (or perhaps ovulation) (Papanicolaou and Traut, 1943) could be "read," 36 smears were taken. The classification III down to I represents grades of increasing senility.

Total number of vaginal smears	36	
Grade III, mainly squamae	1	Adult
Grade IIIM, menopausal clumping	12	Adult
" " mixed, spinosum, squamae, and deep cells	7	Increasing senility
" II (spinosum cells) (40 μ diam.)	9	Increasing senility
" I (small basal cells)	7	Increasing senility

TABLE IV.—*Changes in Vaginal Smears after Vitamin E*

No. and Class	Grade	Dose (mg.)	Effect
47 Radium menopause	IIIM (adult)	4,116	I—i.e., depressed
176 " "	III (full adult)	1,400	II?I—i.e., depressed
466 " " (*Figs.* 1, 2, 3)	Mixed	17,500	IIIM, "luteal clumps"—i.e., higher differentiation
736 *X*-ray menopause	II	14,000	IIIM—i.e., a higher differentiation
743 " "	Mixed	25,200	IIIM—i.e. (very full); almost stilboestrol effect; differentiated
615 Hysterectomy and both ovaries removed	II (vaginitis)	42,000	IIIM—i.e., a higher differentiation

Only six out of 36 smears therefore showed definite alteration in maturity, and this parallels the lack of clinical change after alpha-tocopherol. Case 47 (Table IV) had had dienoestrol up to the beginning of treatment with alpha-tocopherol, and the smears simply depict a sudden loss of ovarian hormone or its equivalent, dienoestrol. Case 466 is mentioned later, since here the development of an intensely clumped smear not only resembled a pregnancy smear but on laparotomy a luteal cyst was discovered (Fig. 4). The changes in Case 736 were quite sharp, so that a guess was hazarded that this patient might menstruate, and, as described below, this actually happened.

Effect of Vitamin E on the Cervix

Thirty-four speculum (Cusco) examinations following doses up to 60 g. of alpha-tocopherol failed to show any increase in bulk, softening of the portio, or increased mucus secretion. Four out of five cases with bleeding punctate spots on the portio, however, were cured by vitamin E; in three this was part of the general healing of the vaginal mucosa.

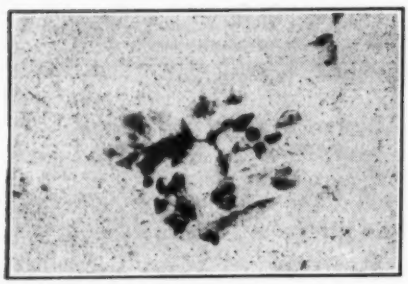

FIG. 1.—Case 466. Radium menopause one year. Small "castration" cells mixed with more mature squamae. *Stain:* Papanicolaou and Traut.

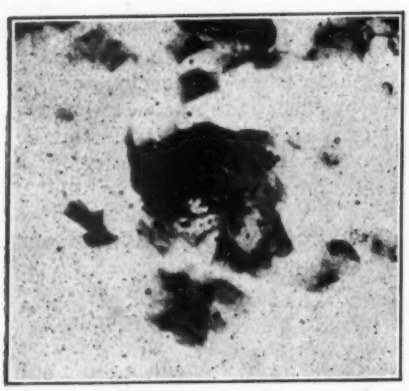

FIG. 2.—Case 466. After 4.5 g. vitamin E. Heaped up smaller cells with larger squamae emerging from deeper layers. This smear resembles mid-pregnancy or the "luteal" phase.

Twenty-six cell-smears were taken before and after treatment, but there was no sharp alteration with use of vitamin E. The motley collection of cells typical of a menopausal cervix persisted—namely, leucocytes, endocervical cells, long (120 μ) fibre cells, and so on. There was no sudden diminution in the number of cells and their replacement by clear mucus such as follows stilboestrol therapy.

FIG. 3.—Case 466. After 17.5 g. vitamin E. Haemorrhagic luteal cyst coexisted. Intermediate cells apparently being desquamated in sheets.

FIG. 4.—Case 466. After 17.5 g. vitamin E. Corpus luteum distended with blood.

It is clear, therefore, that neither the cervix nor its secretion or cytology is altered by massive doses of vitamin E. It may be, however, that just because it does not stimulate cell division and mucus secretion vitamin E may prove to be safer than stilboestrol in the control of flushings which follow irradiation of the pelvis.

Urethral Smears after Vitamin E

Although no patient had urinary symptoms, Hanley's (1944–5) work in menopausal urethritis and trigonitis, and Zuckerman's (1940) observations on the male macaque urethra, suggested that it might be worth while to observe the cytological changes in the urethra.

A dry swab often fails to pick up urethral cells, and only 21 specimens were obtained. A typical well-differentiated smear contains ovoid epithelial cells about 40 μ in diameter; free nuclei, leucocytes, and small clumps of flattened squamae complete the picture. Fourteen typical (differentiated) smears were not altered by vitamin E—i.e., there was no further building up or desquamation of the epithelium. The changes observed in seven smears are shown in Table V.

As in the vagina, therefore, there is no sharp reaction in all urethral smears, and it is possible that the changes observed were the result of faulty technique—e.g., in failing to pick up cells. Only in Cases 736 and 47 was a corresponding change observed in the vagina—namely.

TABLE V.—*Changes in Urethral Smears*

No. and Class	Dose E. (mg.)	Urethral Smear	
		Before	After
263 Radium menopause	3,360	Small undifferentiated cells	Larger, differentiated
45 " "	3,400	Degenerate epithelial cells (? poor fixation)	Loss of leucocytes (inflamed introitus also healed at this time)
47 " "	4,116	Normal smear	Degenerate epithelial cells. (Effect of loss of dienoestrol?)
736 *X*-ray menopause	14,000	Scanty cells	Abundant large differentiated cells
743 " "	25,200	Granular debris	Many adult transitional cells
754 " "	28,000	Scanty debris	Well-differentiated cells; free nuclei
466(*b*) Radium menopause	42,000	Debris	Adult cell smear

maturation, Case 736; senility, Case 47. From this small number of specimens, therefore, it seems possible that vitamin E may cause development and desquamation of the urethral epithelium, although in most cases no cellular alteration is detectable.

Case Reports

Dermatitis and Uterine Bleeding After Vitamin E

Case 1.—Mrs. A, aged 66, developed a generalized itching dermatitis which spared only her face. In the neck the skin became raised in silvery folds, but in the abdomen the rash was rather blotchy and red. Twelve years previously the patient had panhysterectomy with supporting vaginal radium for carcinoma of the corpus, and for a year previously she had suffered from intense pruritus. The vulva was excoriated and had many small areas of lichen simplex. Under vitamin E the vulvar condition almost completely healed. The labia majora and introitus became soft and elastic, but after 16 weeks (36,640 mg. alpha-tocopherol) the rash stopped treatment. The generalized skin condition took eight weeks to settle, but the vulvar pruritus and vulvitis did not relapse, and a year later the patient was practically symptom-free although on examination four very small areas of vulvar excoriation were present.

Post-menopausal Luteal Cyst

Case 2.—A widow aged 42 (No. 466) had radium menopause 10 months ago. Three months ago a 10-weeks course of stilboestrol (1 mg. b.d.) was completed with temporary control of flushing and no withdrawal bleeding. After 5.4 g. of alpha-tocopherol she had 12 days' uterine bleeding preceded by breast-tingling and dysmenorrhoea. Flushings, however, persisted almost unabated, and treatment was continued for 43 days, with control of her flushings. After 17 g. of vitamin E (49th day) she developed sudden right iliac pain with nausea and vomiting. Laparotomy revealed a normal appendix but a left luteal cyst distended with blood. The uterus on its peritoneal aspect resembled a coarse type of liver cirrhosis, being irregular and nobbly to the touch.

Histologically, the luteal cyst from the left ovary was of simple haemorrhagic type, measuring 2 in. by ¾ in. (5×1.8 cm.) (Fig. 4). The right ovary (10 months after radium) contained no recent follicles or corpora lutea but numerous corpora albicans. Vaginal smears: Figs. 1 to 3 show the movement in the cell pictures under vitamin E. No further uterine bleeding followed removal of the right and most of the left ovary, although flushings recurred and were once again controlled by vitamin E (31 g. in 35 days).

"Collapse" of the Breasts

Case 3.—(No. 725.) Aged 46. After 54 g. of alpha-tocopherol the patient complained that her breasts felt slack. Unfortunately we were unable to compare the size of the breasts before and after treatment, but it seems likely that little change in size had occurred. (They were small and pendulous.) No corresponding alteration in cell smear was observed.

Resumption of Menstruation

Case 4.—(No. 736.) Aged 44. *X*-ray castration one year ago. This patient began to menstruate five weeks after 14 g. of vitamin E. Unfortunately she also had completed a course of 20 mg. of amphetamine sulphate, so that it is doubtful which drug (if any) caused resumption of bleeding. Premenstrual curettings showed intense stromal vascularity and simple gland formation.

Comment

Vitamin E can apparently control severe menopausal flushing in more than 50% of cases, and, although not quite inert, its activity on the genital tract in no way compares with that of stilboestrol.

How vitamin E brings about its therapeutic effect on menopausal flushings is quite obscure, and will probably remain so until the mechanism which causes flushing is understood. This lack of knowledge of the therapeutic action of vitamin E applies to other fields of medicine (*Symposium on Vitamin E*, 1939; *Lancet*, 1949) where alpha-tocopherol has been on trial—e.g., in the treatment of primary amenorrhoea (Massenbach and Heinsen, 1948, 1949; Massenbach, 1949), cardiovascular disease (Shute *et al.*, 1948a, 1948b), abortion (Vogt-Moller, 1933), and so on.

When it is available in a cheaper form alpha-tocopherol may replace natural oestrogens and stilboestrol in the control of menopausal symptoms, for, even if only 60% of cases respond, the worry of oestrogen-withdrawal bleeding and the (theoretical) risks of genital cell-stimulation are avoided.

Summary

Vitamin E in the form of alpha-tocopherol temporarily relieved severe menopausal flushing in 30 patients (64%) and failed in 17. The dose required is variable, but averaged 18.5 g. over 37 days (£7 per cure).

Failures did not respond to prolonged and heavy doses, but were quickly relieved by stilboestrol.

Of 17 cases followed up after successful treatment 5 remained cured, 12 had further flushings.

Vitamin E is not an aphrodisiac, but dyspareunia may be relieved in time by the healing of senile lesions in the lower genital tract.

Vitamin E produces no sudden change in the clinical appearance of the lower genital tract, although prolonged and heavy dosage seemed to cause healing in 50% of senile vulvar and vaginal lesions.

Vaginal smears seldom alter, and no parallel exists between cell maturation and the cure of symptoms.

The cervix is not stimulated to mucus secretion.

Cell changes were observed in 7 out of 21 urethral smears.

Side-effects were few: one case developed dermatitis; two cases menstruated, one developing a haemorrhagic luteal cyst.

I am grateful to Professor H. N. Lloyd, Professor Dugald Baird, Dr. James Hewitt, and Dr. Carl Crooke for advice in preparing this report. My thanks are also due to Sister M. Scottwell and to Miss M. E. Attwood, who is responsible for the histology and photomicrographs. Messrs. Roche Products, Ltd., Welwyn Garden City, kindly helped us with gifts of ephynal (alpha-tocopherol).

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TREATMENT OF DUPUYTREN'S CONTRACTURE WITH VITAMIN E

BY

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Since the preliminary report (Thomson, 1949) on the effect of vitamin E in a case of Dupuytren's contracture further cases have come under review and have yielded promising results. In fact, the general response has been so good that to assert that vitamin E has a specific effect on Dupuytren's contracture does not appear to be unduly reckless. The mode of action is unknown, but the work of Steinberg (1946) on the action of the tocopherols on fibrous tissue renders a relationship a little less mystical.

Reports on the success of this treatment have not been unanimous but are inclined to be in its favour. Steinberg (1946) produced the first paper on this subject and described the effects of massive doses of vitamin E on seven cases of Dupuytren's contracture. In six of these cases the contracture disappeared and the sclerodermatous condition of the skin changed to a normal state. One case failed to respond, and this was attributed to the fact that the patient suffered from early portal cirrhosis. In such cases the blood vitamin E level has been shown to be low and large doses of vitamin E are not absorbed. All these cases were treated with a daily dose of 300 mg. of vitamin E orally over a period of 7 to 53 days. Scott and Scardino (1948) discussed six cases treated with 300 mg. of mixed tocopherols or 200 mg. of "ephynal" daily. One case showed marked improvement, three moderate improvement, and two no change. Wrigley (personal communication, 1949) treated three cases with 400 mg. of "ephynal" a day; there was a definite response in two cases and none in the third.

On the other hand, Langston and Badre (1948) treated five cases with the large doses of vitamin E recommended by Steinberg without any demonstrable result. Parsons (1948) treated one case with 300 mg. a day for over 100 days and reported no objective change, although the patient thought he could open one of his fingers a little more freely. Recently, King (1949) described 13 cases treated with 300 mg. of ephynal a day without result. Four of the cases developed hitherto unreported toxic manifestations, which made further treatment impossible. Four other patients were sure they had gained improvement, but none was seen. The longest period of treatment lasted eight weeks.

Present Series

In this series of 13 cases of Dupuytren's contracture involving 22 hands all cases except one were treated with ephynal, four 50-mg. tablets being the daily dose. The minimum length of time that any case has been under treatment is 12 weeks; the majority have been under treatment for 20 weeks. It was notable that the excepted case above and the one previously reported (Thomson, 1949) were treated with wheat germ oil in a weekly dose of 30 mg. and responded dramatically in two weeks, whereas in the cases treated with ephynal a response was unusual within six weeks and common at about eight weeks.

The initial response was usually subjective in character and the patients variably stated that "the bands feel softer," that "there seems to be a little more movement in the fingers," or that "the pain in the palm has gone." Thereafter, improvement clinically started to take place, and progress was steady, with end-results as described below.

The hands were divided into three groups, according to the type and severity of the contracture.

Group A : Early Cases.—In these the disease was of short duration, the palmar bands and nodules were present to a moderate degree, and the fingers were not contracted closer than 90 degrees towards the palm. Ten such hands

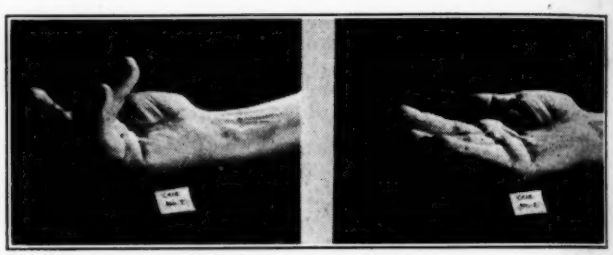

FIG. 1.—Case 1 (*a*) before vitamin E; (*b*) after vitamin E.

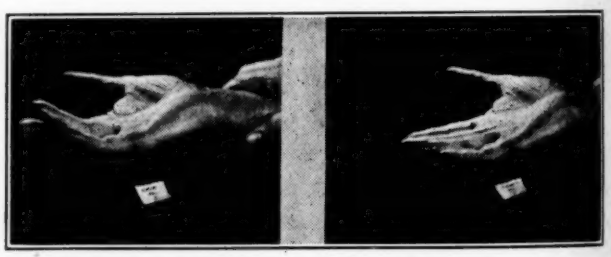

FIG. 2.—Case 3 (*a*) before vitamin E; (*b*) after vitamin E.

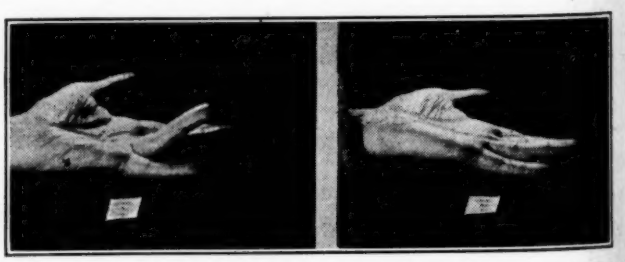

FIG. 3.—Case 6 (*a*) before vitamin E; (*b*) after vitamin E.

were involved. Five responded very well, and full extension of the fingers was restored after the hypertrophied palmar fascia had softened and almost disappeared. Three are still under treatment, and there is every indication that full extension will eventually be obtained in these as well. The remaining two hands had no loss of extension when first seen, and the administration of ephynal has caused some absorption of the palmar masses. The contractures in this group of cases have been so alleviated that additional or alternative surgery has not been considered.

Group B : Late or Chronic Cases.—Here the disease was of long duration, the thickening of the palmar fascia was gross, and the affected fingers were fixed in the palm. All eight cases in this group derived benefit from the administration of ephynal. The palmar masses softened and formed palmar bands running to the appropriate fingers. In addition there was increased movement of the fingers themselves which permitted closer inspection of the palms. The progress was slow, however, and it appeared that a considerable time would have elapsed before an acceptable result could be obtained by the use of ephynal alone. As the palmar bands now invited division, this was carried out in four hands with excellent results. The first hand was treated by simple division of the bands at the bases of the fingers, the medial three being involved. The final result (Fig. 4, c) was only fair so far as full extension was concerned. Nevertheless, the patient was pleased, as he had not used his hand for over two years and has now returned to his former occupation of shifting heavy packing-cases in a store. He has been kept on ephynal until the time of writing, and the sectioned bands have continued to absorb slowly. The other three hands were treated by sectioning the bands in two places—in the palm and at the base of the finger—with better results. Full extension was obtained with all fingers except where joint changes precluded this. The skin deficiency in the palm was made good by skin-grafting, and that at the base of the fingers by Z-plasty or skin-grafting.

FIG. 4.—Case 7 (*a*) before vitamin E; (*b*) after vitamin E; (*c*) after division of digital bands.

Group C : Old Operated Cases with Recurrence.—Four of these cases were treated with the routine dosage of ephynal. In all, the process of recurrence was halted: in two cases some extension was regained, but in the other two degenerative joint changes and scarred skin have prevented much improvement.

Comment

The results obtained in this series correspond with those reported by Steinberg (1946), with the exception that the rate of response has not been so rapid. This is somewhat offset by the lower dosage of ephynal employed. It is noteworthy that the observers who obtained negative results on the dosage recommended by Steinberg (1946) did not get any objective response after two months' treatment in most cases. However, at the time the treatment was abandoned a number of cases reported symptoms of improvement identical with those recorded in this present series, and it is a matter for speculation that continued treatment might have produced more favourable results.

There was no doubt that the four cases in group B eventually operated on were of a gross type, and surgery alone presented a difficult problem; indeed, two of them had been offered amputation as the only practical method. Steinberg (1947) suggested that in the more chronic cases surgery might be required, with the oral administration of vitamin E in addition. This forecast has been well substantiated with these four cases so treated and already described. This method of treatment has much to commend it when compared with treatment by surgery alone, involving prolonged anaesthesia and wide skin undermining in order to remove adherent masses of palmar fascia.

None of the toxic effects noted by King (1949) were in evidence in this series. Most of the cases have had a routine daily dose of 200 mg. of ephynal for five months or more, and many of these patients have stated in opposition to the above that the drug has had a tonic effect upon them.

The relative merits of the natural wheat-germ oil and the synthetic ephynal have not been investigated, but the lone case treated with the former certainly reacted more quickly.

Although the mode of action of vitamin E in Dupuytren's contracture is not recognized, a specific action is at least suggested by two factors. First, in several cases treated acute pain was experienced in the palmar fascia, and in one case marked swelling and tenderness developed before the contracture began to respond. Secondly, Vogelsang *et al.* (1947), in discussing the effect of vitamin E in heart disease, came to the conclusion that, among other vascular effects, scar tissue was invaded by fresh blood vessels, whereby it became softened and relaxed. That a similar phenomenon may occur in Dupuytren's contracture does not seem outside the bounds of possibility.

I wish to thank Dr. Fred Wrigley for his interest and help with this investigation, and to Roche Products Ltd. for their kindness and generous supply of ephynal.

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The National Council of Social Service provides a useful guide to the Welfare State in the new edition of its book, *Public Social Services.* Information is summarized on the National Health Service, National Insurance, employment of disabled persons, education, and many other topics. The handbook includes an interesting chapter on the administration of justice and how free legal aid and advice are obtained. Addresses of the Ministries and organizations concerned with the various services are given throughout. The book may be obtained from the council at 26, Bedford Square, London, W.C.1, for 5s. (paper covers) or 7s. 6d. (cloth).

POLYCYTHAEMIA WITH LEUCOERYTHROBLASTOSIS

BY

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Few cases of leucoerythroblastic anaemia following on polycythaemia have been described in this country (Stone and Woodman, 1938; Vaughan and Harrison, 1939). The term "leucoerythroblastic anaemia," or, better, leucoerythroblastosis (as there may be no anaemia), is used to describe a condition characterized by the presence of immature red and white cells in the peripheral blood, and is due to or associated with replacement of the bone marrow by some other tissue. It is usually classified as follows.

Primary.—(*a*) *Infantile:* osteosclerosis fragilis generalisata (marble bones). This is congenital and may be familial.

(*b*) *Adult:* osteosclerosis; myelofibrosis; agnogenic myeloid metaplasia; and aleukaemic megakaryocytic myelosis. In all probability these last are different names for or different aspects of the same condition. If it were possible to examine a large enough sample of bone marrow during life it might be found that fibrosis and osteosclerosis, pronounced myeloid and erythroid activity, and megakaryocytic excess were all occurring coincidently at different sites. Splenomegaly and, less often, lymphadenopathy may be present.

Secondary or Symptomatic.—Carcinomatosis of bone; multiple myelomatosis; Hodgkin's disease; and lipoidoses. The anaemia may be normocytic or macrocytic. The white cell count may be high or low. The immature cells, the presence of which is an essential part of the disease, are said to be derived from the heterotopic foci in the spleen, liver, kidney, etc. These tissues, it is stated, are incapable of retaining the cells until complete maturation results. Thrombocytopenia may be present. The splenomegaly is due to myeloid metaplasia, although infarcts may add to the enlargement.

Radiographic changes characteristic of the disease have been described—i.e., irregular increased density of the spongiosa of long bones and throughout the flat bones, as well as decreased density of the cortex of long bones (Vaughan and Harrison, 1939). The interpretation of these radiographs requires some experience, and must be compared with controls of the same age and sex. The trephine biopsy will in many cases confirm the diagnosis.

The object of this paper is to record two further cases of leucoerythroblastosis, both of which presented with polycythaemia. The two patients are alive at the time of writing.

Case 1

A married woman with two children first attended hospital in May, 1936, at the age of 32, with a history of having noticed a lump in the left subcostal region one year previously. It had gradually increased in size and had been accompanied by pain on exertion during the previous five months. The only other illness was migraine for 20 years. Examination showed her to be of slim build, cyanosed, with the spleen enlarged to the umbilicus, and the liver enlarged two fingerbreadths below the costal margin. Blood pressure 120/90; van den Bergh indirect reaction faintly positive. A blood count confirmed polycythaemia (see Table I).

July, 1936.—Admitted to hospital; polycythaemia persisted; fractional test meal showed low-acid curve; red-cell fragility test revealed a commencing haemolysis in 0.55% saline, complete in 0.3%; occasional nucleated red cells seen. Course of deep *x*-ray therapy to spleen and lumbar spine.

TABLE I.—*Case 1. Blood Counts*

Date	R.B.C. (Thousands per c.mm.)	Hb %	W.B.C. (per c.mm.)	Varieties of Leucocytes %									Platelets (per c.mm.)	Remarks
				Myeloblasts	Premyelocytes	Myelocytes	Metamyelocytes	Unsegmented polys.	Polymorphs	Eosinophils	Basophils	Lymphocytes	Monocytes	
4/5/36	7,620	82	7,000	—	—	—	—	—	85·0	—	0·5	14·0	0·5	
18/7/36	7,405	116	30,000	—	—	—	—	1·5	81·0	1·5	0·5	13·0	2·5	50 normoblasts per c.mm.
5/8/36	8,000	136												Deep *x* rays
11/8/36	7,565	124												Deep *x* rays
6/4/37	5,560	116												
25/10/37	5,345	108	3,700											
9/5/38	4,965	98	12,600											
17/5/39	3,795	84	9,400											
31/7/40	3,845	92	14,600	—	—	—	—	1·0	70·0	2·0	0·5	20·5	6·0	Few normoblasts
16/10/42	3,775	78	12,000	8·5	—	4·5	—	4·0	68·5	1·5	—	13·0	—	Punctate basophilia 240 normoblasts per c.mm.
11/7/45	4,400	86	12,400	—	2·0	6·5	—	8·0	61·5	—	1·0	17·0	4·0	Some normoblasts
25/4/46	4,040	80	9,100	—	—	2·0	—	12·0	67·0	—	—	15·0	4·0	270 normoblasts per c.mm.
16/6/48	4,140	78	11,100	0·5	1·0	3·0	3·0	—	78·5	1·5	—	10·5	2·0	237,800 Occasional normoblasts. Reticulocytes 2·4%
29/6/48	3,860	74	12,100	1·5	2·0	3·5	9·5	21·5	50·0	—	0·5	9·5	2·0	4 normoblasts per 100 w.b.c.
11/8/48	4,220	71	19,500	1·0	1·0	6·0	4·0	13·0	61·0	2·0	1·5	8·0	2·5	256,000 2 normoblasts per 100 w.b.c.

April, 1937.—No serious symptoms; spleen smaller; haemoglobin 116%.

October, 1937.—Better; haemoglobin 108%.

May, 1938.—No symptoms; haemoglobin 98%.

May, 1939.—Following deep *x*-ray therapy, had amenorrhoea for two years, since when menstruation has been heavy and irregular. Pale; haemoglobin 84%. Seen by Sir Beckwith Whitehouse, who thought *x*-ray therapy may have produced defective luteinization, and recommended progesterone therapy.

July, 1940.—Slight continual uterine haemorrhage for three months; haemoglobin 92%, with a few nucleated red cells present; referred to gynaecology department, where no pelvic cause of bleeding was found.

October, 1942.—Recent pain over splenic area, worse on exertion. On examination: spare, healthy-looking; spleen enlarged to left iliac fossa; liver and glands not enlarged; blood pressure 130/70; leucoerythroblastic anaemia present.

July, 1945.—Health fairly good since October, 1942, but has noticed progressive enlargement of the spleen.

April, 1946.—Admitted to hospital with further aching pain in left flank; amenorrhoea for three years. Spleen enlarged to left iliac fossa and tender on bimanual examination; blood

pressure 160/90. Radiographs of bones of forearms show osteoporosis; serum calcium 8.6 mg. per 100 ml.; serum phosphorus 3.6 mg. per 100 ml. Leucoerythroblastic anaemia present. Surgical belt supplied to support huge spleen.

June, 1948.—Admitted to hospital. Exacerbation of severe continual pain over spleen for one month, made worse by movement or deep breathing. Pale; spleen enlarged to both iliac fossae and very tender on palpation; leucoerythroblastic anaemia present. Platelets 238,000; reticulocytes 2.4%; radiograph of long bones showed osteoporotic appearance of upper half left humerus; sternal-marrow puncture gave a picture not unlike that present in the peripheral blood. A diagnosis of myelofibrosis was made clinically, and sternal biopsy was performed with a view to confirming this, since radiographs of long bones were indefinite. The biopsy was reported on as follows: "These small fragments of sternal tissue show diffuse fibrotic changes with occasional isolated megakaryocytes—very suggestive, if this is representative, of myelofibrosis."

Case 2

A married woman aged 64 first attended hospital in 1924, complaining of pain in the splenic region; a diagnosis of polycythaemia vera was made and *x*-ray therapy given. Attended regularly for eight years and was free from symptoms until 1942. No records available up to this date.

August, 1942.—Pain in splenic region for two months; spleen enlarged to umbilicus and tender; blood pressure 155/90. Red blood cells 4,700,000; normoblasts present (see Table II).

April, 1944.—Slight ache over spleen for three weeks. Red blood cells 4,465,000.

September, 1944.—Patient noticed increasing size of left side of abdomen, but otherwise felt fairly fit; spleen enlarged as far as left iliac fossa; liver enlarged below umbilicus; red blood cells 7,970,000. Admitted to hospital and further course of deep *x*-ray therapy given to spleen, followed by phenylhydrazine therapy. Further *x*-ray therapy given in May, 1945.

June, 1946.—Blood count satisfactory, but in December, 1946, again markedly polycythaemic. Further deep *x*-ray and phenylhydrazine therapy given.

October, 1947.—Purpura on legs and arms; platelet count 270,000 per c.mm.; blood count satisfactory except for numerous unsegmented polymorphs.

May, 1948.—Admitted to hospital with eight weeks' history of lassitude, swelling of ankles, and noticeable enlargement of abdomen; rubicund facies; few petechiae of limbs; abdomen distended, with everted umbilicus and shifting dullness; spleen enlarged to right iliac fossa; blood pressure 145/95. Blood count showed mild hypochromic anaemia with numerous immature leucocytes, a few normoblasts, and 54,000 platelets per c.mm.

It was considered that this indicated the development of either myelosclerosis or aleukaemic leukaemia. Sternal puncture was twice performed and the picture was essentially that of the peripheral blood; the bone seemed soft and gritty on puncture. These findings are typical of myelofibrosis. Bleeding time 5½ minutes; clotting time 4½ minutes; prothrombin 55% of normal. Serum proteins 6.52 g.%; serum uric acid 5.6 g.%; serum alkaline phosphatase 7 units; blood urea 27 mg. per 100 ml. A barium swallow radiograph showed some irregularity of oesophageal wall consistent with varices; radiographs of sternum and femora were normal.

On June 17, 1948, the patient left hospital against advice. The diagnosis was considered to be myelofibrosis following polycythaemia vera, with cirrhosis of liver.

Comment on the Cases

Case 1 presented as a case of polycythaemia rubra vera and was treated with deep *x* rays. The blood count gradually fell, and once below normal never rose again. This suggests that the case was one of primary myelofibrosis presenting as polycythaemia (see Vaughan and Harrison, 1939). It is of course possible that the patient had previously had polycythaemia rubra vera and had already developed myelofibrosis when first seen. Certainly, in June, 1948, the sternal biopsy demonstrated myelofibrosis The corpuscular fragility was increased (admittedly slight), which coincides with the findings of Vaughan and Harrison

TABLE II.—*Case 2. Blood Counts*

Date	R.B.C. (Thousands per c.mm.)	Hb %	W.B.C. (per c.mm.)	Varieties of Leucocytes %										Platelets (per c.mm.)	Remarks
				Myeloblasts	Premyelocytes	Myelocytes	Metamyelocytes	Unsegmented polys.	Polymorphs	Eosinophils	Basophils	Lymphocytes	Monocytes		
17/8/42	4,700	92	7,100	—	—	—	—	10·0	56·5	1·0	2·0	21·5	9·0		1,000 normoblasts per c.mm.
14/4/44	4,465	118	6,600												
15/9/44	7,970	110	10,900	—	—	—	—	10·0	66·0	1·0	2·0	15·0	6·0		Few normoblasts
2/10/44	8,500	99	11,100	—	—	—	—	7·5	74·0	—	—	14·0	4·5		Deep *x* rays. Phenylhydrazine
5/3/46	6,120	112	9,200	—	—	—	—	—	61·0	2·0	5·0	27·0	5·0		
2/6/46	4,340	84	3,100												
6/12/46	7,100	128	8,200												
2/1/47	8,030	118	4,600												Deep *x* rays
8/1/47	6,210	110	6,200												
27/1/47	6,330	98	70,000												
21/4/47	5,300	92	60,000												
31/10/47	5,610	106	5,600	—	—	—	—	16·5	30·0	2·5	3·5	30·0	17·5	270,000	
29/11/47	6,470	116	4,900	—	—	—	—	—	58·0	1·0	—	36·0	5·0		Petechial rash
5/3/48	5,400	100	5,600	—	—	—	—	—	63·0	—	5·0	26·0	6·0	165,000	1 normoblast
7/3/48	5,370	90	60,000												
20/5/48	4,370	76	4,100	2·5	2·0	5·0	12·0	16·0	34·5	1·5	5·0	17·0	4·5	54,000	2 normoblasts per 100 w.b.c.
8/6/48	4,220	74	4,000	2·5	6·5	5·0	13·5	13·0	20·5	1·0	1·5	36·5	—	32,000	

Case 2 was diagnosed as a case of polycythaemia rubra vera. From 1924 until 1947 this patient had a typical polycythaemic count. In May, 1948, she showed many of the features of leucoerythroblastosis associated with myelofibrosis—i.e., leucopenia, presence of immature red and white cells in the peripheral blood, gross splenomegaly, and a presumably non-functioning bone marrow. Myelofibrosis was suspected on the grounds that sternal puncture revealed a soft gritty bone, and the material, when examined, showed a picture not unlike that found in the peripheral blood. Such a terminal event in polycythaemia rubra vera has been recorded.

Discussion

The pathogenesis of the primary variety is obscure Vaughan (1934) suggested that the undifferentiated mesenchyme develops predominantly along one line to produce fibroblasts or osteoblasts. There is no attempt to explain why this should happen. Myelofibrosis and osteosclerosis have followed benzol and phosphorus poisoning. The

picture of osteosclerosis with leucoerythroblastosis can occur in fluorosis. *X* rays have been known to produce fibrosis of the marrow; and Joan Ross (1932) describes the effects of gamma radiation over a period of three years. The marrow showed hyperactivity of the myeloid and erythroid cells with a marked increase in megakaryocytes. The nutrient vessels showed endothelial thickening and intravascular thrombi. It is not beyond possibility that repeated doses of deep *x* rays over many years may produce the picture of myelofibrosis in polycythaemia rubra vera.

Thanks are due to Professor A. P. Thomson and Dr. O. Brenner for permission to publish these cases; and to Dr. J. L. Stafford for his report on the sternal biopsy.

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A CASE OF WEIL'S DISEASE, WITH TESTS FOR LIVER FUNCTION

BY

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Familiarity with Weil's disease during the war has resulted in several publications in the English and American literature. Although jaundice is usually a marked feature of this disease, there is no record of liver-function tests. The following case is therefore described, together with the result of tests for liver dysfunction and for other biochemical disturbances. These were of great help in excluding the diagnosis of acute hepatic necrosis, which was made on admission. It is hoped that this will stimulate physicians who have greater opportunities for studying this disease to investigate its chemical pathology, and to deduce from their findings evidence concerning the site of tissue damage.

Case Report

The patient, a plumber aged 58, was admitted on April 13, 1949. Up to a week previously he had been working on a boiler in a meat-pie factory in which fat was rendered down. Seven days before admission he had a rigor; this was followed by another two hours afterwards. Four days later he noticed he was yellow, and he began to vomit incessantly. There was no abdominal pain.

On examination he was a very ill man, dehydrated, with subsultus tendinum, deep jaundice, and a generalized purpuric eruption. The mucosae were pale. He was afebrile; the pulse rate was 90, the blood pressure was 130/80, the heart sounds were faint, and there were basal crepitations. The liver was not palpable. There was some free fluid in his abdomen, and his stools were pale. Three days later he developed a swinging temperature up to 102° F. (38.9° C.), which was maintained for five weeks and subsided by lysis, and which did not respond to penicillin, 250,000 units six-hourly intramuscularly for 10 days.

He was given 5 pints (2.34 litres) of fluid by mouth, 3 pints (1.7 litres) of "casydrol" by intravenous drip transfusion, 6 ml. of "campolon" intramuscularly, 500 mg. of ascorbic acid, and 15 mg. of vitamin K daily. Later he developed a urinary infection with *Pseudomonas pyocyanea*, for which he was given 4 g. of streptomycin daily by injection for five days.

Subsequent Course.—His rash cleared up in three days; the jaundice had faded by the first week in July, but he was pyrexial for a month. However, he remained mentally in a state of stupor, with considerable clouding of consciousness, marked loss of memory for recent events, and disorientation in time and place. Some measure of recovery occurred, but when his wife took him on May 31 he was able to sit out in a chair, though he showed a good deal of mental deterioration, with lack of all initiative and poor memory. A letter from his wife on July 27 stated that his general condition had improved, but his legs were weak and useless and his mental state poor.

Investigations

Agglutinations.—*L. icterohaemorrhagiae:* April 20, 1:1,000; April 29, 1:1,000; May 5, 1:3,000. *L. canicola, nil. Salm. typhi, Salm. paratyphi* A, *Salm. paratyphi* B, and *Br. abortus, nil.*

Blood Counts.—Haemoglobin: April 14, 59%; May 9, 59%; May 23, 72%. Red cells: April 14, 3,750,000; May 9, 3,020,000; May 23, 3,500,000. White cells: April 14, 25,000 (P. 77%, L. 21%, M. 1%); May 9, 25,000 (P. 89%, L. 10%, M. 1%); May 23, 18,000 (P. 75%, L. 25%, M. 4%).

Serum Proteins.—April 24: total, 5.75 g.% (albumin 4.2, globulin 1.5; A/G ratio 2.7:1). May 5: total, 5.5 g.% (albumin 3.7, globulin 1.8; A/G ratio 2.05:1).

Liver-function Tests.—Alkaline phosphatase: April 24, 10.7 units; May 5, 16.3 units; May 23, 12.8 units. Thymol turbidity: April 24, 1.5 units; May 5 and 23, 1 unit. The Takata–Ara and colloidal gold tests were negative.

Urine.—April 19 and 25: specific gravity, 1010; albumin, sugar, and bile salts, *nil*; bilirubin was in excess on April 19 and urobilin was present on April 25. On April 25 there were 10 cells per field and *Ps. pyocyanea* was found. On May 30 there were many pus cells and *Ps. pyocyanea* was still present. There were no spirochaetes.

Haemolysins.—On May 30 no cold agglutinins were present, and Coombs's direct and indirect tests were negative.

On April 14 the serum diastase amounted to 320 mg. per 100 ml. (normal, 70–150 mg.). On April 22 the blood urea was 27 mg. per 100 ml., the alkali reserve 49 volumes, and the serum calcium 8.6 mg. per 100 ml. On May 10 the blood urea was 35 mg. per 100 ml. and the alkali reserve 43.9 volumes. On April 22 the blood sugar totalled 148 mg. per 100 ml., and the serum cholesterol 177 mg. per 100 ml. (free, 80 mg.; ester, 97 mg.).

The diagnosis was based on the presence of jaundice, the rash, the patient's occupation, and the rising titre of agglutinins.

Comment

The morbid pathology of the liver in Weil's disease is described by Hutchinson *et al.* (1946). They say that the liver in their cases was usually of normal size, with masses of bile pigment in the biliary canaliculi of the centrilobar part of the liver lobules, and emphasize the absence of necrosis. On the other hand, Heringman and Phillips (1947) mention considerable disorganization of the liver pattern with moderate vacuolization and swelling of cells and the formation of continuous cords of liver cells instead of normal groups of two or three cells.

In the case described by Jackson and Oleesky (1946) there was no macroscopic hepatic necrosis; there were scattered areas of fatty degeneration and areas of regeneration, with enlarged binucleated liver cells. They mention that Walch-Sorgdrager (1939) refers to the frequent misdiagnosis of acute yellow atrophy, as happened in our case.

Our case on admission, being afebrile at the time and extremely ill and toxic, closely resembled the picture of acute hepatic necrosis. The finding of normal plasma proteins and Takata–Ara, thymol turbidity, and colloidal gold tests was therefore of distinct value in excluding this diagnosis, and would seem to rule out any overwhelming degree of parenchymal damage.

The absence of urobilin in the urine in the early stages would seem to point to an obstructive element in the jaundice such as might be caused by the bile pigment masses in the small canaliculi that Hutchinson *et al.* described; however, the alkaline phosphatase was never above 16.3 units. Unfortunately the Coombs tests were done too late to exclude a haemolytic factor. Apart from the complicating *Ps. pyocyanea* infection there was no evidence of renal damage. The blood urea remained normal, and there were no casts or red cells in the urine. The serum diastase value of 320 mg. per 100 ml. would appear to suggest disturbance of pancreatic function.

The mental state of the patient is worthy of passing comment. There was never any sign of meningitis leptospirosa. Three possible theories about causation are: first, that the condition was due to cerebral damage by the organism or its toxins; secondly, that it was due to the severe jaundice; and, thirdly, that the haemorrhagic state present at the onset in the skin was also present in the brain; this is, I think, the most likely.

Summary

A case of Weil's disease, with liver-function tests, is described.

An attempt is made to correlate these with previously described accounts of the pathology of this condition.

Other interesting features of the case are briefly dwelt on.

My thanks are due to Dr. A. G. Signy and the staff of the laboratories of St. Mary Abbots Hospital and the Archway Hospital for the pathological reports.

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PRIMARY LYMPHOSARCOMA OF APPENDIX OCCURRING IN CHILDHOOD

BY

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Lymphosarcoma arising in the appendix is rare; only seven cases occurring in childhood have been published. In a majority of such cases the children have had symptoms suggestive of appendicular disease. In the following case the patient had no such symptoms, and the clinical picture which presented was therefore of special interest.

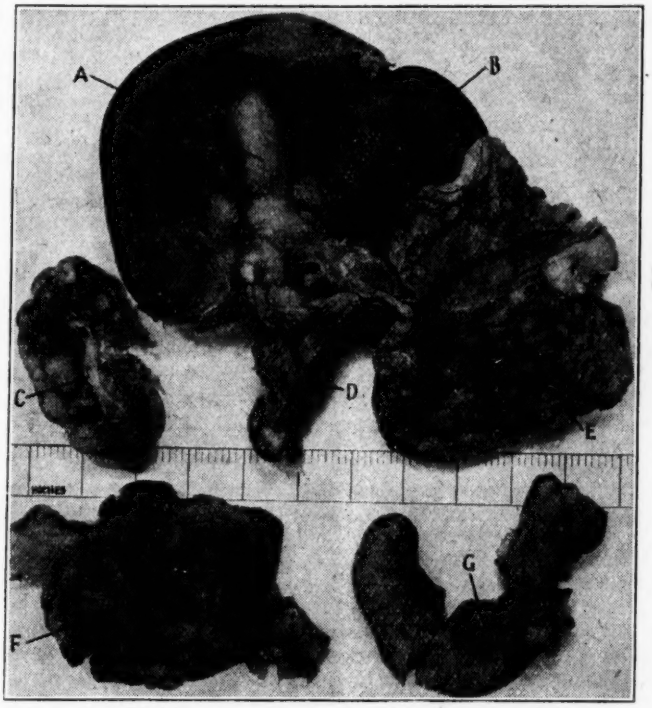
Case Report

A boy aged 6 years 9 months was admitted to hospital on October 1, 1948. The child had been well until four weeks before admission, when he was immunized against diphtheria. Since then he had been "off colour" but had attended school. Three days before admission he complained of pain in his chest and right thigh, and vomited once. His mother noticed a swelling on his left temple on the following day; but there had not been any loss of weight or other symptoms. There was nothing relevant in the family history or in the child's previous personal history.

On examination his temperature was 100° F. (37.8° C.), pulse 80, and respirations 20. The child's general condition was poor; he was very irritable and complained of pains in all his joints. A swelling on the left temple was noted and there were palpable glands in the left axillary and cervical regions. Abdominal examination revealed tenderness in both iliac fossae, but there were no palpable masses. Routine clinical examination did not show any further abnormal features.

For the first three days the temperature varied between 98.4 and 102° F. (36.9 and 38.9° C.). On the fourth day his temperature fell and remained normal until the eighth day, when it rose to 103° F. (39.4° C.). At this time the left knee-joint was slightly swollen. There was no cardiac enlargement, but a soft apical systolic murmur could be heard. The abdomen was rather large and doughy, with dullness in both flanks. The liver was enlarged one fingerbreadth below the costal margin and the tip of the spleen was felt. The kidneys were not palpable and no other abdominal masses were found. There were no abnormal signs in the central nervous system.

Radiographs of the chest, abdomen, and skull, a Mantoux test (1:10,000 dilution), blood culture, and Widal reactions



A = Gall Bladder; B = Liver; C = Kidney; D = Pancreas; E = Stomach; F = Ileal Mass; G = Appendix.

were all negative. The erythrocyte sedimentation rate was 50 mm. in one hour. The blood picture was: haemoglobin, 68%; red cells, 3,920,000; white cells 5,000 (polymorphs 54%, myelocytes 7%, metamyelocytes 14%, lymphocytes 20%, monocytes 3%, eosinophils 2%). An intravenous pyelogram, the blood Wassermann reaction, and a blood-urea estimation were all negative. No Bence-Jones proteose was present in the urine, and the stools did not contain either visible or occult blood.

The pyrexia was maintained despite penicillin and salicylate therapy. The liver increased in size to two fingerbreadths below the costal margin. The swelling over the left temple had increased in size and was now 1 in. (2.5 cm.) in diameter; it was tender and gave the impression of deep fluctuation. No further lymphatic gland enlargement developed. The child's appetite remained good, but despite this he was obviously becoming more wasted. His bowels were normal and he had no vomiting. An irregular soft mass, thought to be faeces, was felt in the right iliac fossa on the thirteenth day. The rectum was found to be loaded with soft brown faeces, but there was no palpable mass. Just below the ninth costal cartilage a small nodule was felt on the enlarged liver. There were no signs

of free fluid in the peritoneal cavity. The abdominal girth was 21¼ in. (54 cm.). The blood pressure was 130/70 mm. Hg.

The abdominal mass became progressively larger and firmer, but signs of obstruction were not observed. His pallor increased, and despite a blood transfusion he died 32 days after admission. Before he died the child developed proptosis of the left eye and a left-sided facial weakness.

Post-mortem Findings

The appendix measured 12 cm. in length and 4 cm. in diameter. It was horn-shaped, with a smooth white serosal surface (see Fig.). On section it consisted throughout of a uniform white homogeneous tissue in which the lumen could not be distinguished. This condition ceased abruptly at the root of the appendix. There were widespread deposits of a similar tissue throughout the body, affecting practically every organ.

Histology.—The greatly enlarged appendix consisted of sheets of cells resembling small lymphocytes which obliterated the lumen and destroyed muscle, leaving only traces of widely separated muscle fibres in the external layer. Occasional mitoses were to be seen. Silver staining showed very scanty reticulin fibres traversing the tissue, particularly in relation to small vessels: large tracts of cells were devoid of reticulin. The other structures containing obvious tumour showed similar histological changes. The spleen, pancreas, and thyroid, although normal to naked-eye examination, showed a slighter degree of infiltration.

Table Showing Details of Reported Cases

Reported By	Age in Years	Sex	Presenting Symptoms	Duration	Operation	Follow-up	Operation Findings
Apitz (1933)	8	Male	Died from uraemia	Approx. 6 weeks	None	None	Appendix 5 cm. in circumference and 17 cm. in length
Capecchi .. (1927)	8	..	Mild abdominal pain in right lower quadrant	1 month	Appendicectomy	None	Distal third of appendix tumour size of hen's egg
Carnelli .. (1931)	10	..	Pain in right lower quadrant	2 months	Appendicectomy, excision of left part of caecal wall	Asymptomatic 14 months later	Appendix with tumour at proximal end 2·5 cm. long by 0·5 cm. broad: the caecal wall was infiltrated
Friend (1926)	9	Female	Recurrent cramp-like abdominal pain in right lower quadrant	3–4 weeks	Appendicectomy (high unrotated caecum)	Death 1 month later	Hard, firm, thick appendix 15 cm. long
Knox (1945)	4	Male	Intermittent pain right lower quadrant with nausea, vomiting, and moderate diarrhoea	2 months	Appendicectomy	Asymptomatic 15 months later	Appendix 9·5 cm. long, 18 mm thick
Rohdenburg (1919, 1921)	4	Not given	History suggestive of acute appendicitis with pre-operative diagnosis of intussusception	No time stated, but apparently acute	Appendicectomy with partial removal of caecum	No recurrence after 10 months	New growth involving proximal third of appendix and extending into caecal wall
Warren .. (1898)	6	Male	Intermittent pyrexia and pain in right lower quadrant	1 month	Resection of part of ileum, caecum, and appendix	None	Appendix size of thumb
Present case	6¼	..	Pyrexia and vague ill-health. No symptoms referable to abdomen	1 month	None	None	Appendix 12 cm. long by 4 cm. broad

Discussion

Knox (1945) gave details of a boy aged 4 years with lymphosarcoma arising in the appendix, and he reviewed 16 cases of undisputed primary lymphosarcoma of the appendix, of which five had occurred in childhood (Warren, 1898; Rohdenburg, 1919; Friend, 1926; Capecchi, 1927; Apitz, 1933). A further search of the literature revealed one other case in childhood (Carnelli, 1931). So far as can be ascertained no such case occurring in childhood has been reported in British literature.

In all reported cases, except that of Apitz, the presenting symptoms were suggestive of acute or subacute appendicitis. Laparotomy was performed and a tumour involving the appendix found and removed. The age, sex, presenting symptoms, duration, nature of operation and findings, and period of follow-up are shown in the accompanying Table.

In our case the uniform homogeneous appearance of the appendicular lesion, with complete replacement of the inner layers of the wall of the appendix by lymphosarcomatous tissue, suggests that the disease arose there, and is in contrast with another large mass in the ileum, which seems to have been formed by the fusion of several submucous lesions similar to those seen elsewhere in the intestinal wall.

Lymphosarcoma occurs more commonly in males, and in the reported cases the ratio of males to females was 3 to 1. Munson and Mann (Guthrie, 1948) believe that the outlook is good after surgical removal of a solitary tumour. Knox (1945) suggests that radiotherapy may be expected to be helpful in prolonging life and may even cure if the disease is localized. Sugarbaker and Craven (1940) state: "The occasion of a primary site in the gastro-intestinal tract regardless of sporadic reports of cures seems to carry an unfortunate outlook. None of the patients whose stomach or small intestines were involved lived for five years, the average survival period being 6.6 months."

We should like to thank Professor N. B. Capon for his help and advice; Dr. W. E. Crosbie, medical superintendent, Alder Hey Children's Hospital, Liverpool, for permission to publish this case; and Dr. E. G. Hall for the pathological reports.

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The National Insurance Advisory Committee has been asked to consider and report on preliminary draft regulations concerning students from outside the United Kingdom who during a vacation become temporarily employed in Great Britain. The effect of the regulations is that, in cases approved by the Minister of National Insurance, contributions under the National Insurance scheme will not be required unless the students are continuously resident in Great Britain for 26 weeks. Industrial injuries contributions remain payable. Copies of the preliminary draft of these regulations (the National Insurance (Residence and Persons Abroad) Amendment Regulations, 1950) can be bought for 1d. from H.M. Stationery Office or any bookseller. The committee will consider written objections to them if sent before January 3, 1950, to the Secretary, National Insurance Advisory Committee, 6, Curzon Street, London, W.1.

SURGICAL MANAGEMENT OF THE AGED

A SURVEY OF RESULTS OF MAJOR SURGERY IN 99 PATIENTS OVER 70

BY

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"The days of our years are threescore years and ten: and if by reason of strength they be fourscore years, yet is their strength labour and sorrow; for it is soon cut off, and we fly away."

The average age of the population is increasing, and is likely to do so. It therefore seems reasonable to survey the results of surgery in those patients who are over the age of 70 years, the one-time allotted span of life.

During the thirty months January, 1947, to June, 1949, 1,609 patients were admitted to the 32 surgical beds of one surgical unit at a London teaching hospital. Of these 1,609 patients 131 were over the age of 70—seven were not submitted to surgery, 24 were submitted to minor surgery, and 99 were submitted to major surgery. It is instructive to compare this situation with those existing 10 and 20 years ago. Table I shows in a comparable number of admissions the numbers of patients over 70 seen and the number of these patients submitted to major surgery. Applying the rules of significance to these figures, it will be apparent that more patients over the age of 70 were admitted in 1947–9 than was the case 20 years ago, and that more patients over the age of 70 were submitted to major surgery than was the case 10 years ago.

TABLE I

Period	Total Admitted	No. Over 70	No. of Patients Over 70 Submitted to Major Surgery
Jan., 1927, to Nov., 1929	1,609	82 (5·1%)	40 (49%)
Jan., 1937, to Sept., 1939	1,609	108 (6·7%)	61 (56%)
Jan., 1947, to June, 1949	1,609	131 (8·1%)	99 (75%)

It is the 99 patients in our series submitted to major surgery that we wish to discuss. Distribution between the sexes was almost equal—49 males and 50 females. Fifteen patients were admitted as emergencies; 17 patients (6 females and 11 males) died before discharge from hospital.

Operations Performed

Operations on the Head and Neck

Section of sensory root, fifth cranial nerve	1
Hemiglossectomy	2
Block-dissection glands of neck	1
Section thyroglossal cyst	1
Subtotal thyroidectomy	1
Excision of large rodent ulcer of nose and skin graft	1

Operations on the Trunk and Upper Limbs

Radical mastectomy	5
Lymphangioplasty	1

Hernias and the Scrotum

Incisional hernia	1
Inguinal hernia without strangulation	4
Strangulated inguinal hernia repair	2
Strangulated inguinal hernia with resection	1
Femoral hernia repair	8
Strangulated femoral hernia, resection, and anastomosis	1
Operations on scrotum and contents	2
Incarcerated umbilical hernia	2

Intra-abdominal Operations

Colostomy	7
Closure of colostomy	4
Laparotomy	10
Laparotomy and colostomy	5
Laparotomy, colostomy, repair of inguinal hernia, and dorsal slit	1
Laparotomy and cholecystenterostomy	1
Laparotomy and suprapubic cystostomy	1
Cholecystostomy	1
Cholecystectomy	1
Cholecystectomy and choledochotomy	1
Suture of perforated peptic ulcer	1
Gastrotomy	1
Gastrostomy	1
Subtotal gastrectomy	3
Subtotal gastrectomy and colectomy	1
Gastro-enterostomy	2
Transabdominal repair of diaphragmatic hernia	1
Transthoracic oesophago-gastrostomy	1
Appendicectomy	1
Caecostomy	1
Right hemicolectomy	2
Ileo-transverse-colostomy	2
Resection sigmoid colon	1
Resection sigmoid colon and colostomy	1
Perineal excision of rectum	1
Perineal excision of rectum and colostomy	1
Abdomino-perineal excision of rectum	7
Perineo-abdomino excision of rectum	3
Excision of ovarian cyst	1

Operations on Prostate and Anal Canal

Haemorrhoidectomy	2
Prostatectomy	2
Transurethral resection of prostate	5

Operations on the Lower Limbs

Above-knee amputations	8
Below-knee amputations	1
Manipulations of ankle	2
Excision of popliteal aneurysm	1

A number of these patients underwent minor surgical procedures requiring further anaesthetics.

Preparation of the Patient for Operation

A full clinical examination was made, with special reference to the heart and lungs. After the age of 70 it is only natural to find signs of wear and tear in the cardio-vascular and respiratory systems. Of these 99 cases 60 showed clinical evidence of abnormalities in one or both of these systems:

Gross hypertension (i.e., B.P. 180/100 or more)	14
Hypertension or signs of myocardial insufficiency	13
Signs of myocardial insufficiency	6
Hypertension and/or myocardial insufficiency and signs and symptoms of respiratory disease	15
Respiratory disease alone	12

In addition, arteriosclerosis, anaemia, and wasting were very common findings.

Operation was delayed in 13 cases; the reasons for delay were:

Patient in bed too long	1
Poor nutrition	2
Dehydration	1
Dehydration associated with low percentage of haemoglobin	1
Low percentage of haemoglobin	2
Abdominal distension	2
Respiratory disease	4

Pre-operative Measures Taken.—The usual treatment for shock was practised according to the severity. Throughout this series of cases it has been customary to encourage

early rising after operation. Therefore, when a patient had been confined to bed for a period, operation was delayed while he was made ambulant so that he could be sat out of bed immediately after recovery from the anaesthetic. If possible, general nutrition was improved. In some cases it was necessary, as in a case of achalasia of the cardia, to give a high-calorie diet through an oesophageal tube. Vitamin intake was maintained when necessary by intramuscular injection of vitamin C and "heparglandol B," and "synkavite" was given as a routine in all cases undergoing surgery of the biliary system. Dehydration was corrected by intravenous saline or glucose-saline; blood transfusion was given pre-operatively in all cases which showed a low haemoglobin percentage. Distension increases the risk of operation and also the difficulty. Where the operation was not in itself likely to be a decompressing procedure, operation was delayed if distension was present while a Miller–Abbott tube was passed. A Ryle's tube was passed on all patients who were vomiting pre-operatively. All cases with respiratory disease and all cases about to undergo intra-abdominal operations were given pre-operative breathing exercises unless the case was an emergency. Coughing and postural drainage were encouraged in those who had productive coughs; penicillin inhalations were given and systemic penicillin and sulphonamides started. In some cases this treatment was carried out for one week before operation. Digitalis therapy was given to those with auricular fibrillation.

Premedication.—All cases received a hypodermic injection of 1/100 gr. (0.65 mg.) of atropine half an hour before operation. In addition, those with marked pain received 1/6 gr. (11 mg.) of morphine. Hyoscine (scopolamine) was purposely avoided because of its tendency to produce disorientation and restlessness in the aged, and morphine was avoided or kept to a minimum in order not to depress the vital capacity.

Anaesthesia

The choice of anaesthetic was determined to a large extent by the type of operation to be performed and the general condition of the patient. Of the 134 anaesthesias, 81 were for intra-abdominal and 53 for extra-abdominal procedures. The agents used for the various types of operation are shown in Table II.

TABLE II.—*Anaesthetic Used*

	Intra-abdominal (Including Intrathoracic)	Extra-abdominal (Including Intracranial)	Total
Curare and light anaesthesia	52	3	55
Spinal and local	10 (7 spinal, 3 local)	1 (spinal)	11
Thiopentone, gas, oxygen, ether, Gas, oxygen, ether	16	16	32
Thiopentone and cyclopropane	3	7	10
Thiopentone, gas, oxygen, and trilene	—	20	20
Bromethol, gas, oxygen, and trilene	—	2	2
Thiopentone	—	4	4
Total	81	53	134

Thiopentone.—When thiopentone was used for induction it was injected very slowly, because the circulation time in the aged is prolonged. Also, owing to the low basal metabolic rate in the elderly, the elimination of thiopentone in the body is slower, and liver and kidney damage may be present. Hence only very small doses were used—rarely more than 0.5 g.

Curare.—Curare in the form of *d*-tubocurarine chloride was mostly used when relaxation was required. The initial dose was usually 10 mg., and the final total dosage depended on the agent used to maintain light anaesthesia; with ether, approximately half the usual dosage of curare is required. The closed-circuit carbon-dioxide-absorption technique was used as a routine for cases receiving curare; the basal oxygen requirement in the aged is low, but at the same time suboxygenation must be avoided. This often entailed assisted respiration for the whole of the operation, as some degree of stagnant hypoxia was already present owing to a poor myocardium and a sluggish peripheral circulation.

Spinal Analgesia.—This method was used only if the site of operation was subumbilical, if the patient's blood pressure was within normal limits, and if the condition of the chest did not warrant an inhalational method.

Local Analgesia.—This method was used in three cases: in an emergency laparotomy with faecal vomiting, in an emergency caecostomy in a patient who was in cardiac failure, and in a patient with incarcerated incisional hernia who was in early cardiac failure.

Intubation.—Intubation of the trachea was carried out in all abdominal cases. If vomiting was a pronounced symptom, as in cases with bowel obstruction, intubation was performed with a cuffed intratracheal tube, and a sucker was at hand to keep vomitus clear of the larynx. The Ryle's tube was kept in place throughout the operation and aspirated from time to time.

Position on the Operating Table.—Old people are prone to osteoarthritis, and their skins withstand pressure badly. For these reasons their position on the operating table must be carefully supervised, a support provided for the back, shoulder-pieces well padded, and hands not placed under the buttocks.

Resuscitative Measures.—Patients suffering from pre-operative shock or dehydration continued with blood or saline throughout the operation. If a long operation was anticipated a slow blood drip was started at the beginning of the procedure. If signs of shock developed during an operation blood or plasma was administered. All such cases returned from the theatre to the ward with their intravenous drips still running.

Post-operative Measures

As soon as the patient was sufficiently recovered from the anaesthetic, he or she was sat up and encouraged to cough, to take deep breaths, and to move the legs. The services of a trained physiotherapist were found to be invaluable in this respect. Five-minute inhalations of carbogen every hour were a useful adjunct to physiotherapy. The patient was sat up in a chair within 12 hours of operation in all cases in which it was practicable. Where the likelihood of respiratory complication was great, even patients undergoing gastric suction and intravenous drip therapy were so treated. They sat in a chair for increasing periods each day from then on. Continuous gastric suction and intravenous therapy were practised for 48 hours after operation in all cases undergoing an intra-abdominal operation which might result in paralytic ileus. Intravenous therapy and suction were stopped only when intestinal movements were well established. Watch was kept over the bladder to ensure that retention with overflow did not occur. The usual measures to combat retention were practised up to 24 hours, after which catheterization was performed if necessary. Where retention was persistent and due to prostatic hypertrophy, an indwelling catheter was used until the patient was considered fit for a transurethral resection, and penicillin or a sulphonamide was administered. Routine testing of urine for chlorides was practised from the first post-operative day.

Post-operative Therapy.—All drugs administered pre-operatively were continued in the post-operative period—i.e., penicillin, sulphonamides, or digitalis. In all major abdominal procedures, and where sepsis was a danger, prophylactic penicillin and sulphonamides were administered. Where cardiovascular complications occurred digitalization was instituted. In all cases of respiratory complications and in those cases in which coughing was difficult owing to tenacious sputum, mistura sodii chloridi composita (*N.W.F.*) was found to be invaluable.

(*e*) *Retention of Urine.*—Four cases of retention of urine required transurethral resection of the prostate.

(*f*) *Pressure Sores.*—These occurred in three cases.

(*g*) *Cardiovascular System.*—Auricular fibrillation (electrocardiogram showed poor myocardium in one case), 3; auricular flutter, 1; incipient cardiac failure necessitating digitalis therapy, 1.

The 17 fatal cases are analysed in Table III.

TABLE III.—*The Patients Who Died*

	Case No.	Age	Sex	Operations Performed	Anaesthetic	Previous Condition	Cause of Death
Respiratory	1	82	F	Removal of carcinoma of ovary	Thiopentone, 0·2 g., N_2O, oxygen, ether	History of previous pneumonia and chronic cough	Bronchopneumonia
	2	70	M	Strangulated inguinal hernia with resection of gut (E.)	Thiopentone, 0·3 g., N_2O, oxygen, ether	B.P. 200/120; severe arteriosclerosis	Intercurrent lobar pneumonia
Cardiac	3	74	M	(1) Laparotomy and colostomy (2) Perineo-abdominal resection of rectum	(1) Thiopentone, 0·5 g., curare, N_2O, oxygen (2) N_2O, oxygen, ether		Cardiac failure. Post mortem: brown atrophy of heart muscle
	4	74	M	(1) Laparotomy and colostomy (2) Perineo-abdominal resection of rectum	(1) Thiopentone, 0·25 g., curare, N_2O, oxygen, ether (2) Thiopentone, 0·2 g., curare, cyclopropane	B.P. 230/120; severe arteriosclerosis	Hypertensive heart failure
	5	73	M	Repair of right inguinal hernia and orchidectomy	Thiopentone, 0·7 g., N_2O, oxygen, ether	B.P. 180/100; some cough; senile Parkinsonism	Hypertensive heart failure
	6	70	F	Lotheissen's operation for Richter's hernia (E.)	Thiopentone, 0·4 g., cyclopropane, curare	B.P. 210/110; asthmatic heart enlarged	,, ,,
	7	85	M	Prostatectomy	Cyclopropane	Fibrillating under digitalis; moist sounds both bases	Cardiac failure
	8	72	M	Caecostomy (E.)	Local	Pulsus alternans; moist sounds both bases	,, ,,
	9	71	F	Above-knee amputation (E.)	Thiopentone, 0·15 g., cyclopropane	B.P. 190/115; mild diabetic	Fibrillated: congestive heart failure
	10	70	M	Gastrostomy	Thiopentone, 0·25 g., curare, cyclopropane		Cardiac failure; toxaemia from subphrenic abscess; carcinoma of oesophagus
Secondary Emergency Operations	11	71	M	(1) Gastro-enterostomy (2) Laparotomy (E.)	(1) Thiopentone, 0·65 g., curare, cyclopropane (2) Local	Previous history of pneumonia; scattered rhonchi	No cause for death; terminal bronchopneumonia
	12	70	M	(1) Perforated peptic ulcer (E.) (2) Subtotal gastrectomy (E.) (3) Resuture abdominal wound (E.)	(1) N_2O, oxygen, ether (2) Thiopentone, curare, N_2O, oxygen, trilene (3) Curare, thiopentone, cyclopropane	B.P. 130/70; severe blood loss before second operation	General peritonitis from leaking duodenal stump and terminal bronchopneumonia
	13	80	F	(1) Subtotal gastrectomy (2) Ileo-transverse colostomy (E.)	(1) Curare, thiopentone, 0·7 g., cyclopropane (2) Thiopentone, 0·5 g., cyclopropane	B.P. 190/95. B.P. 60/? before second operation	General peritonitis from leaking duodenal stump
Carcinomatosis	14	70	F	Cholecystostomy (E.)	N_2O, oxygen, ether	Obstructive jaundice, diabetic	Carcinomatosis secondary to carcinoma of pancreas. Died day after operation
	15	70	M	Laparotomy only	Thiopentone, 0·5 g., curare, N_2O, oxygen, ether	B.P. 140/94	Died six weeks after operation; carcinomatosis
	16	72	M	,, ,,	Curare, N_2O, oxygen, ether	B.P. 160/115; severe arteriosclerosis	Died 7 days after operation; carcinomatosis with paralytic ileus
	17	74	F	,, ,,	Thiopentone, 0·4 g., N_2O, oxygen, ether	B.P. 260/100	Died 3 months after operation; asthenia due to carcinomatosis

(E.) = Emergency operation.

Post-operative Complications

(*a*) *Wounds.*—Mild sepsis, 10; severe sepsis, 2; haematoma, 9; disruption, 1.

(*b*) *Thrombophlebitis.*—Due to intravenous drip therapy, 4; not due to intravenous drip therapy, requiring anticoagulant therapy, 3.

(*c*) *Chest.*—Major respiratory complications: severe bronchitis, 5; atelectasis (one case of bilateral basal collapse following a spinal analgesic), 5; bronchopneumonia, 3; pulmonary embolism, 1. It is to be noted that all these patients underwent an abdominal operation, and 12 of the 14 had pre-existing respiratory disease.

Minor Respiratory Complications

Under this heading are included all patients who had a raised respiratory rate for not more than three days after operation and cases of mild bronchitis. There was no relation to the type of operation, and of the 17 who suffered this complication 15 had pre-existing respiratory disease.

(*d*) *Intra-abdominal Complications.*—General peritonitis due to leaking duodenal stump, 2; persistent vomiting producing a salt-lack syndrome, 1.

Disposal of the Aged Patient

With the present shortage of hospital and convalescent beds, disposal of the aged patient requires some consideration. Such patients are not so fit as younger ones to return rapidly to normal domestic routine. Often they live alone and have no relatives to go to. Discharge from hospital therefore has frequently to be delayed. The almoner's department can often help with such cases by providing home helps or making suitable alternative arrangements. However, this problem is a very real one, and will require serious consideration in the future. Convalescent homes already have waiting-lists. At the present time the patient with an inoperable carcinoma who has been in hospital for a laparotomy often occupies a hospital bed until he dies. This is an undesirable situation in view of the great demand on hospital beds.

Conclusions

More patients over the age of 70 are submitted to major surgery than was the case 10 years ago.

Age alone is not a contraindication to surgery of any magnitude.

Care must be directed especially to the cardiovascular and respiratory systems.

Sepsis is a greater risk, and for this reason penicillin and sulphonamide therapy should often be used as a prophylactic measure

The aged should never be allowed to lie in bed.

Disturbance of the electrolyte balance is not well tolerated. This is well illustrated in three patients who required second operations as emergencies: in all of them vomiting or blood loss had grossly disturbed the fluid balance. All three patients died.

The commonest cause of a major chest complication is pre-existing respiratory disease in association with an abdominal operation. These complications are rarely fatal.

The commonest cause of death is cardiac failure arising in a hypertensive patient irrespective of the type of operation.

Some steps must be taken in the future to facilitate the care of the aged post-operative patient who does not require further active surgical treatment in a hospital bed. A comprehensive medical service must make better provision for this.

Summary

The results of major surgery in 99 patients over the age of 70 are surveyed.

The types of operation performed are enumerated.

The pre-operative management is considered.

The choice and administration of anaesthetic are discussed.

The post-operative management is outlined.

The 17 fatal cases are considered in detail.

Conclusions are drawn concerning the practice of surgery in the aged.

A plea is made for more adequate provision for the care of the convalescing aged patient.

All these cases were admitted under Sir Cecil Wakeley and Mr. E. G. Muir, to whom we wish to express our thanks for permission to survey these cases and for their guidance at all times. We are grateful to Dr. Vernon Hall and other members of the anaesthetic staff who administered some of these anaesthetics. We also thank Miss Fern and her staff for the kind co-operation of the Record Office.

Of nearly 7 million dollars spent on tuberculosis research in the United States in a 12-months' period during 1947–8, about two-thirds were expended for the study of drugs in tuberculosis treatment. A survey undertaken by the National Tuberculosis Association showed that the greatest expenditure on tuberculosis research was by official agencies, with a total of nearly 4 million dollars, of which 3 million were allocated to chemotherapy investigations. Following closely behind the official agencies were manufacturing firms, with appropriations of over 2 million dollars. Research by firms manufacturing *x*-ray equipment was also carried out. Universities expended nearly 200,000 dollars on tuberculosis research, with only 4,500 dollars allocated to chemotherapy. It is pointed out, however, that a large part of the studies financed by other agencies are actually carried out in institutions with university affiliation. Dr. E. R. Long, director of the medical research and therapy department of the National Tuberculosis Association, has stated that if streptomycin had not appeared so promising a drug "it is safe to say that much less money would have been expended for chemotherapeutic research, and much less, accordingly, for all research," but he emphasizes that streptomycin research has disclosed the need for more fundamental research in tuberculosis. "Had streptomycin proved as successful as the most optimistic enthusiasts anticipated," he stated, "had it proved, for example, as effective as penicillin in certain types of pneumonia, it is probable that interest in basic investigation on tuberculosis would have declined. Actually, however, streptomycin research has raised more problems than it has answered, and the new problems, such as the nature of the antibiotic mechanism and the reason for bacillary resistance to the drug, can be solved only by fundamental laboratory research."

Medical Memoranda

Chronic Progressive External Ophthalmoplegia

The idiopathic form of chronic progressive external ophthalmoplegia is rare enough to warrant a brief description of the following case.

CASE REPORT

The patient was a man aged 39 who was born in Rumania and had wandered about Eastern Europe and the Middle East. The family history revealed nothing significant. He had been in England since 1947. In 1933 he developed suppurating cervical glands; in 1935 he had pneumonia, and in 1942 typhoid fever. While he was in Egypt, at the age of 36, he noticed drooping of his left eyelid. In April, 1949, he came to hospital complaining of dizziness, double vision, and cough. There was marked ptosis of the left eye. Asymmetrical external ocular palsies were present, and the movements of the eyes were as follows:

	Right Eye		Left Eye	
Outwards	8°	20°	14°	16°
Inwards	12°		2°	
Upwards	30°	55°	2°	27°
Downwards	25°		25°	

The pupils were equal and circular, and reacted normally to light. On ophthalmoscopic examination the fundi were normal; an error of refraction (vision: R. 6/12, L. 6/36) was easily correctable, and perimetry showed very slight symmetrical diminution of the peripheral parts of the visual fields in each eye. No abnormality of other cranial nerves was observed, and all reflexes and sensations were unimpaired. Examination revealed no other physical signs.

The cerebrospinal fluid was normal, and the blood pressure was 130/80. Radiographs of chest and skull were normal, and the blood Wassermann reaction and Kahn test were negative. To exclude myasthenia gravis a therapeutic test was done (2.5 mg. neostigmine + 1/100 gr. (0.65 mg.) atropine), but, as expected, no improvement in the eye movements was observed

COMMENT

In 1900 Wilbrand and Saenger studied 32 cases of chronic progressive external ophthalmoplegia and considered the condition to be a distinct clinical entity. The characteristic features, as they described them, are as follows: The onset is gradual, usually beginning in childhood, but may be delayed. Ptosis may be the first sign of the disease for a considerable time; years may elapse before there are signs of paralysis of the external ocular muscles, and diplopia may or may not occur. The internal ocular muscles remain normal and the health of the patient is not affected. According to these authors, "It is a striking feature of the affection that no other signs or symptoms develop indicating implication of other organs or other structures of the nervous system." Since the beginning of this century very few cases have been reported which belong to this group.

Altland (1909) described a case in which ptosis of the right eye occurred at the age of 22, and which developed bilateral ptosis (left incomplete) and immobility of both globes at 51. McMullen and Hine (1921) reported three cases, but one was excluded from this group because a subsequent examination revealed disease of other parts of the central nervous system. There are also reports by Langdon and Cadwalader (1928) and Farias (1941).

Fuchs (1890) thought that isolated forms of bilateral ptosis might be cases of primary myopathy. Ayres (1896) reported the disease in a boy whose maternal grandfather also suffered from it. Beaumont (1900) had 12 cases, and not only was there a familial incidence but in some there was an associated weakness in the distribution of the seventh nerve. This involvement of the central nervous system beyond the confines of the oculomotor nuclei is not in conformity with the description given by Wilbrand and Saenger.

The case described by Sandifer (1946), a man of 29, had bilateral ptosis for fourteen years, a complete external ophthalmoplegia, weakness of the orbicularis oculi, and certain cardiovascular changes. Although there was no family history, the resemblance of this case to some of those described by Beaumont cannot be overlooked. Sandifer found that, histologically, biopsy of the external rectus revealed myopathic degeneration, and he suggested that the lesion in chronic progressive ophthalmoplegia separated by Wilbrand and Saenger may sometimes be in the muscle and not in the oculomotor nuclei. Langdon and Cadwalader (1928), in their case of a woman of 81 with bilateral ptosis and almost immobile globes, found that the oculomotor nerves were comparatively small, the cells of the Edinger-Westphal nuclei were normal (this accounting for the internal ocular muscles being spared), but the cells of the remaining portions of the oculomotor nuclei showed some chromatolysis, pigmentation, and shrinkage. It is of interest to note that similar left-sided degeneration in the more proximal levels of the third nucleus was reported by Siemerling (1891) in a case of left-sided congenital ptosis with normal internal and external ocular muscles. This may indicate that the same aetiological factors are operative, whatever these may be, yet the two conditions are clinically distinct. Gowers (1893) speaks of "deficient vital endurance of the structures concerned," and his theory of abiotrophy is generally offered in explanation.

At present there seems to be a tendency to group together all cases of chronic progressive external ophthalmoplegia. Some of these cases may be familial, or they may be of myopathic origin (Nikitin, 1929; Elliott, 1939; Martin, 1939), while others may show evidence of involvement of different parts of the central nervous system in addition to the oculomotor nuclei. But since the prognosis is favourable in the condition separated by Wilbrand and Saenger (so far as the disease remains confined to the oculomotor nuclei), I believe it deserves to remain a distinct clinical syndrome, at least until the pathogenesis is elucidated.

K. K. HUSSAIN, M.D.

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An Unusual Case of Rickets (Fanconi's Syndrome)

There are several atypical forms of rickets, but perhaps that associated with glycosuria, hypophosphataemia, and mild acidosis is the rarest; hence the interest of this case.

CASE REPORT

The patient, a female child aged 11 months, was sent from a maternity and child-welfare clinic to the paediatric out-patient department of the City General Hospital, Stoke-on-Trent, on November 19, 1948, for investigation of glycosuria. The mother reported that the child had been normal and healthy until a few weeks earlier, when increasing thirst had been noted and she had ceased to gain weight. She had become constipated also and was inclined to vomit. The mother was especially concerned because a son had died in 1941, at the age of 6 years, from what was stated to have been "nephritis and uraemia." The mother volunteered the information that he had had "sugar in his water" from the age of 12 months, and that the onset of his illness had been associated with thirst and retardation of growth. Further questioning elicited that the father had died from a renal calculus, the mother herself being apparently normal, as is her only other child, a girl aged 7.

On clinical examination the patient was a pale fragile child, with two teeth, and was able to stand and to say a few words. Her weight was 16 lb. (7.26 kg.). There was evidence of recent loss of weight, and she appeared dehydrated. She had well-marked rickets, with bossing of the skull, rachitic rosary, and thickening of the lower ends of the radii. Her abdomen was distended, and faecal masses could be felt in the left iliac fossa. No abnormal findings were noted in her throat, ears, chest, or in the cardiovascular and central nervous systems.

Special Investigations.—Urine: This showed an acid reaction, a trace of albumin with 1% of sugar (proved to be glucose), an excess of amino-acids, and no ketone bodies; microscopy revealed a few red blood cells, scanty pus cells, and numerous granular casts. *Blood:* Urea varied between 34 and 42.6 mg. per 100 ml.; sugar, 83 mg. per 100 ml.; serum phosphorus, 2 mg. per 100 ml. (normal 4–5 mg.); serum calcium, 9.3 mg. per 100 ml. (normal 9–11 mg.); serum alkaline phosphatase, 10.1 units (normal 3–13); serum acid phosphatase, 3.2 units (normal 0.5–5); plasma proteins, 4.75 g.%; alkali reserve, 50 vols. CO_2%; Wassermann reaction negative. *Radiology:* A straight radiograph of the abdomen and radiograph of the skull and pituitary fossa showed no abnormality, and I.V.P. was deemed inadvisable owing to the child's general condition. A radiograph of the wrists showed decalcification of the bones with rickets. A glucose-tolerance test confirmed the glycosuria to be renal in origin.

COMMENT

The association of rickets, glycosuria, hypophosphataemia, and mild acidosis is extremely rare. The first cases were reported in 1926 by Schier and Stern, others being later reported by Fanconi (1931), by whose name the syndrome is sometimes known, and De Toni (1933).

The aetiology of the condition is uncertain, but it is known to have a familial incidence. It is said to be due to a defect of the renal tubules which renders incompetent the reabsorption of glucose, amino-acids, and phosphates. This explains the increased amino-acids in the urine, the often decreased blood proteins, the glycosuria of renal type, and the hypophosphataemia (the last-mentioned being sometimes the cause of renal calculus). The defect is said to be in the proximal renal tubules, where glucose and phosphates are normally reabsorbed in the form of phosphate esters. Stowers and Dent (1947) have demonstrated on post-mortem material that phosphatase, which is essential for the formation of these esters, is absent from the proximal renal tubules, where it is normally abundant, and

they believe this to be the major defect in Fanconi's syndrome.

The above case seems to be a classical example of the condition, and has several features of note. First, the family incidence : there seems to be no reason to doubt that the child who died in 1941 showed the main features of the syndrome, and it is probable that the father's renal calculus was related to the condition of his children. Unfortunately no notes of either of these cases are available. Secondly, in spite of the fact that the child had received adequate anti-rachitic treatment (fortified cod-liver oil) since birth, she had developed gross rickets by the age of 11 months. Finally, the early age at which diagnosis was possible is of interest.

The condition being a congenital and often hereditary defect of the renal tubules, treatment is unfortunately of little avail.

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Acute Psychosis Caused by Dextro-amphetamine

The following case is of interest because of the small amount of the drug taken.

CASE REPORT

A petty officer stoker mechanic aged 29 reported sick with a five-years history of headaches and depression. His M.O. found no organic cause for the headaches and, in view of the depressive element, prescribed dextro-amphetamine. The patient was given 14 5-mg. tablets and instructed to take two daily. At 6 a.m. on the following morning he was found stuporous on the bedroom floor. He had been incontinent of urine. He was able to state that before retiring he had taken 11 tablets (55 mg.) of dextro-amphetamine. When he regained consciousness in hospital he thought he saw a piece of paper going up the side of the door. He then complained that somebody was putting his finger on the top of the door and taking it away quickly. He also imagined he saw smoke coming through a partly open door, and later in the forenoon he stated that there were flashes of light going across the bed. He had auditory hallucinations at the same time, and he felt annoyed because nobody shared these experiences. Similar hallucinations continued during the remainder of the day. The next morning he was cheerful, co-operative, and relaxed. Consciousness was clear, his thought and conversation were coherent and relevant, and he was not at all depressed or irritable. He was still hallucinated and had come to the conclusion that someone had been arranging these phenomena in order to test his reactions to them. He lacked insight and could not accept any suggestion that he had been hallucinated. He had no further hallucinations after his first morning in hospital, and he developed good insight. His thought and behaviour rapidly became normal and he had no further symptoms except occasional headaches.

COMMENT

The dose taken by this patient appears to be the smallest on record to have precipitated a psychotic state. Probably a larger dose would have been required if he had taken the drug previously and had thereby gained some tolerance. Idiosyncrasy to small doses, resulting in circulatory collapse, is reported by Davies (1937), Norman and Shea (1945), Shorvon (1945), Mutch (1948), Sargant and Slater (1948), and others. Idiosyncrasy was evidently responsible for one of the two recorded fatalities—that of a student aged 25 who collapsed and died after taking 30 mg. of amphetamine sulphate daily for a few days (Smith, 1939). The other death occurred after the accidental ingestion of 40 mg. of amphetamine by a 1-year-old child (Hertzog *et al.*, 1943).

Eight cases are recorded of acute psychosis caused by amphetamine and its dextrorotatory isomer. Young and Scoville (1938) administered amphetamine to two narcoleptics, who both developed a paranoid psychosis after a few weeks. The amount of the drug taken was uncertain, but was of the order of 30 to 40 mg a day. Norman and Shea (1945) report the development of somatic, visual, and auditory hallucinosis in an alcoholic aged 49 who had been taking a daily dose of 250 mg. of amphetamine for five years. Monroe and Drell (1947) describe a further four cases of hallucinations and ideas of reference amongst prison inmates who had been ingesting strips of amphetamine from inhalers. One had taken 93 mg. and another 250 mg. The amount consumed by the other two is not specifically stated, but was probably of the same order, since each inhaler contained 250 mg. of amphetamine base. Schneck (1948) reported visual hallucinations and delusions in a man who had consumed one and a half amphetamine inhalers within 36 hours.

We are indebted to Surgeon Rear-Admiral J. A. Maxwell, C.V.O., C.B.E., F.R.C.S., K.H.S., medical officer-in-charge, R.N. Hospital, Haslar, for permission to publish this case.

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The important effect on stressed "perspex" windows of solutions used for the disinsectization of aircraft is described by Whittingham and Galley in the *Monthly Bulletin of the Ministry of Health and the Public Laboratory Service* (1949, **8**, 186). Some insecticide solutions facilitate the crazing of these windows, a process which manifests itself in the formation of cracks varying from a surface frosting to deep, highly reflecting fissures. This causes a weakness which in pressurized aircraft may lead to the window blowing out in flight—a serious matter for the aircraft and its occupants at high altitudes. Four common insecticides were tested in the laboratory for their effect on stressed "perspex," and a wide variation was demonstrated in the intensity of their action. One solution containing methylene chloride, for example, caused instantaneous crazing when sprayed on to the window material. Whittingham and Galley's findings indicate the importance of consulting aircraft constructors and experts on materials used in aircraft in the development of new insecticides for this use.

Reviews

THE CARE OF THE OLD

Geriatric Medicine. By E. J. Stieglitz, M.D., F.A.C.P. Second edition. (Pp. 773; illustrated. £3.) Philadelphia and London: W. B. Saunders Company. 1949.

Age is Opportunity. (Pp. 118; illustrated. 2s. 6d.) London: The National Council of Social Service, 26, Bedford Square, London, W.C.1.

The two books are symptomatic of the increasing interest in the care and welfare of the aged. In a sense they are complementary, for the first sets out to discuss the diseases from which the aged suffer, with their prevention and their treatment, while the second gives much useful advice and information to those who wish to see elderly persons given the greatest opportunity possible for their own happiness.

Unfortunately, Stieglitz and his 46 co-authors have not made up their minds on what they are attempting to do. As a result, their book does not completely satisfy any one criterion. It is not a textbook of medicine, because it presupposes much fundamental knowledge of medicine; yet it is not a handbook for the doctor who wishes to do something for his elderly patients, because it treats in too much detail of all diseases affecting all patients. It does not limit its lesson to modifications or improvements in the diagnosis and treatment of old people suffering from general disease.

One can except from this generalization the articles written by Stieglitz himself, both on the general approach to and on the philosophy of the medical care of the elderly, and on hypertensive arterial disease From these sections there is much that can be learned and much for the intelligent reader to ponder over. The author comments with a refreshing sanity on the interpretation of a raised blood pressure, pointing out the irrelevance of a single reading and emphasizing the importance of the time factor in prognosis. The instructions for treatment are clear and detailed, and show how the patient with early hypertension can enjoy a reasonable life without being a burden to himself or his relations by reason of a host of dietetic fads and restrictions. Similarly, Monroe's article on diseases of the joints comes near to being a model of clear thinking and wise treatment. His advice on the management of a patient suffering from early rheumatoid arthritis is excellent. He realizes that the hopeless deformities so frequently seen are not inevitable, and gives in some detail his own method of preventing their occurrence.

Few of the other authors go into sufficient detail to make this expensive book of much practical value to the doctor who wishes to do his best for his elderly patients. Old people certainly have their own problems: it is true that there are no major changes in the concept of treatment between the middle-aged and the aged, but the difference between success and failure in this specialty lies in the ability to devise means of overcoming the effects of lengthy illness and even longer deformity. Little attention is given in this book to considering how best to prevent the onset of illness among the elderly, and sufficient emphasis is not laid upon the remarkable capacity for rehabilitation possessed by these people, provided it is realized that the response to treatment will be slow and that much patience will be needed to obtain success. This does not need to be the patience of inertia; the treatment is of interest because of the infinite variety of detail needed to achieve a successful result.

Reference to the occurrence of pulmonary tuberculosis among the elderly is interesting and important, and one wonders how many children have been infected by a loving grandparent suffering from a "touch of bronchitis." But it is surprising to read suggestions for the treatment of Eustachian deafness with radium: experience gained in this country during the war has shown the dangers of this practice.

The handbook issued by the National Old People's Welfare Committee gives good advice to any body, voluntary or municipal, that wishes to take an intelligent interest in the welfare of the elderly. It deals systematically with their wants, and shows how these can best be satisfied. It gives, therefore, indications of how the elderly can be kept in good health, and how they can be prevented from becoming a burden to the community by sinking into a state in which they need to be admitted to hospital for long periods. Regular visiting and the establishment of clubs will not only combat the loneliness which is one of the great dreads of old age, but will enable disease to be recognized while it is remediable. Provision of meals will help to prevent the varied types of malnutrition which are found among the elderly. A useful occupation will keep the mind alert and active, and its provision should help finally to dispel the idea that the aged are incapable of learning new trades. Advice on the setting up of homes and other forms of housing will go far to ensure that the older members of the population shall be housed in as suitable surroundings as their younger countrymen, and will do much to keep them well. This is a useful book that should be widely read.

AMULREE.

HANDBOOK OF FRACTURES

Fractures and Dislocations in General Practice. By John Hosford, M.S., F.R.C.S. Second edition revised by W. D. Coltart, F.R.C.S. General Practice Series. (Pp. 288; 87 illustrations. £1 1s.) London: H. K. Lewis and Co. 1949.

Modern methods in the treatment of fractures, with the necessity for repeated radiographic examination, plaster work, physiotherapy, and other ancillary services, have made it inevitable that most fractures should be treated primarily in the fracture services of the hospitals. More often than not the general practitioner has neither the facilities nor the apparatus for the efficient handling of fractures, other than those of a minor nature. Nevertheless, it would be unfortunate if the family doctor were to lose touch with modern developments in treatment. He may no longer be responsible for the details of the local treatment of the fracture, but very often the general supervision of patients under treatment at the fracture clinic will fall to his care. His advice and opinion will often be sought; and he will be called in if unexpected symptoms should develop in the intervals between the patient's visits to the clinic.

The second edition of this book has been revised considerably to suit the changed conditions that now prevail. It does not set out to teach the practitioner how to treat a fracture: it is designed to give him an up-to-date account of the broad lines on which fractures and dislocations are treated in hospital. The book can be commended for its clear descriptions, accuracy, and conciseness. It should fulfil well the purpose for which it has been designed, and it may prove even more successful as a short handbook for students.

J. C. ADAMS.

NEONATAL MORTALITY

Fetal and Neonatal Death. By Edith L. Potter, M.D., Ph.D., and F. L. Adair, M.D. Revised edition. (Pp. 173; illustrated. £1 10s.) Illinois, Chicago: University of Chicago Press. Great Britain and Ireland: Cambridge University Press. 1949.

All those concerned with the care of the newborn baby have used "Potter and Adair" since it first appeared in 1940. A new and revised edition, which incorporates new work on the Rhesus factor and the effect of rubella upon the foetus, is therefore most welcome. It is of great importance to consider stillbirths as well as neonatal deaths to gain a complete picture of loss of life at this period, and the study of the problem in the necropsy-room or as an exercise in statistics is well described. It is inevitable that the references should be almost entirely to American literature, and it seems strange to find respiratory difficulties at birth discussed without any reference to Barcroft's work. It would be a fascinating task to relate the United States statistics to those of other countries, as Professor C. McNeil did with his Scottish figures in 1942.

The authors' approach to a subject which still requires much exploration is essentially that of pathologists. As will be gathered, the effect of this monograph upon the reviewer is to make him eager to see it much enlarged: it is excellent as far as it goes. ALAN MONCRIEFF.

PATHOGENESIS OF INFECTION

Klinische Infektionslehre. By Professor Felix O. Höring. Second edition. (Pp. 245. M. 18.) Berlin: Springer. 1948.

Professor Höring's *Clinical Study of Infection* is an unusual book. It is an attempt to bridge the gap between bacteriology and immunity on the one hand and clinical medicine on the other. It is not a textbook or a monograph, but rather an essay with pathological physiology as its central theme. Health and illness are taken as abstractions; the host and the parasite are the only concrete realities. The author revolts from the concept of disease resulting from the blind operation of chance, something imposed on the host from outside. The individual cannot be thought of apart from his environment. The relation of the host to the parasite is not one of enmity but essentially an attempt at mutual adaptation with symbiosis as its goal. Medical bacteriology is therefore merely a branch of oecology.

Starting from this thesis, the author examines the different reactions of tissues to the parasite, classifying them into normal, anergic, and hyperergic. He then divides all infectious diseases into three categories: (*a*) the cyclical diseases characterized by a predictable course—incubation period, period of generalization, period of localization in the organs; (*b*) the local diseases, characterized by a focus of inflammation that spreads only by direct continuity and pursues an irregular course; and (*c*) the septic diseases, characterized by an inflammatory focus that is in direct communication with the blood stream, thus enabling the particular types of parasite associated with these diseases to give rise to generalized manifestations. Further subdivision follows, and ten possible courses are described for the infectious process. Each of the infectious diseases is then briefly examined, and classified according to its pathogenesis into one or other of the numerous theoretical categories laid down.

This form of abstractive treatment is perhaps more congenial to the Teutonic than the English mentality, but both clinicians and bacteriologists may find something stimulating in the author's method of approach to a well-worn subject. G. S. WILSON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Sight Light and Efficiency. By H. C. Weston. (Pp. 308. 42s.) London: Lewis. 1949.

The Biology of Mental Defect. By L. S. Penrose, M.A., M.D. Preface by J. B. S. Haldane, F.R.S. (Pp. 285. 21s.) London: Sidgwick and Jackson. 1949.

The Theory of Inbreeding. By R. A. Fisher, Sc.D., F.R.S. (Pp. 120. 10s. 6d.) London: Oliver and Boyd. 1949.

Living Through the Older Years. Edited by C. Tibbitts. Foreword by E. J. Soop. (Pp. 193. 16s.) London: Geoffrey Cumberlege. 1949.

Magnetism. By D. Shoenberg, Ph.D. (Pp. 216. 10s. 6d.) London: Sigma. 1949.

Sinuhe the Egyptian. By M. Waltari. Translated by N. Walford. (Pp. 503. 12s. 6d.) London: Putnam. 1949

Infant Nutrition—Its Physiological Basis. By F. W. Clements, M.D., D.P.H. (Pp. 246. 21s.) Bristol: John Wright. 1949

Clinical Audiology. By M. Saltzman, M.D. Introduction by G. M. Coates, M.D. Foreword by M. S. Ersner, M.D. (Pp. 195. $5.) New York: Grune and Stratton. 1949

Clinical Diagnosis by Laboratory Examinations. By J. A. Kolmer, M.D. 2nd ed. (Pp. 1,212. $12.) New York: Appleton-Century-Crofts. 1949.

Acute Laryngotracheobronchitis. By A. H. Neffson. M.D. (Pp. 197. $5.) New York: Grune and Stratton. 1949.

Fundamental Considerations in Anesthesia. By C. L. Burstein, M.D. (Pp. 153. 30s.) New York: Macmillan. 1949.

Microbiology. By F. C. Kelly, M.S., Ph.D. and K. E. Hite, Ph.D., M.D. Introduction by G. M. Dack, Ph.D., M.D. (Pp. 592. $6.50.) New York: Appleton-Century-Crofts. 1949

Resuscitation and Anesthesia for Wounded Men. By H. K. Beecher, A.M., M.D. (Pp. 161. 40s.) Oxford: Blackwell Scientific Publications. Springfield, Illinois: Charles Thomas. 1949.

Public Health Bacteriology and Parasitology. By C. G. Booker, M.D., D.P.H., L.R.F.P.S. (Pp. 254. 35s.) Johannesburg: Central News Agency. 1949

Les Processus Anatomiques de Cicatrisation des Greffes de Cornée. By J. Babel. (Pp. 63. Swiss francs 8.20.) New York and Basle: Karger. 1950

Précis de Parasitologie. By E. Brumpt. Vols. 1 and 2. 6th ed. (Pp. 2,138. 7,700 francs.) Paris: Masson. 1949

Cardiologie. By D. Routier. (Pp. 365. No price.) Paris: Librairie Maloine. 1949

Ulcers and Eczema of the Leg Sequels of Phlebitis. By H. Bisgaard. Preface by H. Haxthausen, M.D. (Pp. 105. No price.) Copenhagen: Einar Munksgaard. 1948.

Taschenbuch der Praktischen Medizin. Edited by J. Kottmaier. (Pp. 788. M. 24.) Stuttgart: Georg Thieme. 1949.

Die Therapie der Übertragbaren Kinderlähmung. By K. Hofmeier. (Pp. 112. M. 7.50.) Stuttgart: Georg Thieme. 1949.

Lebenserinnerungen aus einer Wendezeit der Heilkunde. Wollen und Schaffen. By E. Hoffmann. (Pp. 403. M. 12.) Hanover: Schmorl and Von Seefeld Nache. 1949

Homöopathische Arzneimittellehre. By A. Stiegele. (Pp. 436. M. 25.) Stuttgart: Marquardt. 1949.

Röntgen- und Radiumphysik für Mediziner. By R. Glocker. (Pp. 275. M. 19.80.) Stuttgart: Georg Thieme. 1949.

Lehrbuch der Chirurgie. By R. Stich and K. H. Bauer. (Pp. 860. M. 60.) Berlin: Springer. 1949.

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VITAMIN B_{12} AND PERNICIOUS ANAEMIA

Vitamin B_{12}, a crystalline anti-pernicious-anaemia factor of great potency, was isolated almost simultaneously in 1948 in this country and in the U.S.A. We have already commented[1] on some of the reports describing its properties and uses. Intramuscular injections of a few microgrammes of this compound, which appears to possess all the activity usually associated with liver extracts, causes remissions in pernicious anaemia, sprue, steatorrhoea, and nutritional macrocytic anaemia. The only other substances which have such a powerful action in minute quantities, though in their case a harmful one, are the radioactive element plutonium and botulinus toxin. Calculation shows that not more than a few hundred molecules of vitamin B_{12} are necessary for the maturation of one red cell. Reports on the use of vitamin B_{12} have so far been confined to small series of patients treated with varied amounts of the vitamin and followed up for very short periods. In this issue of the *Journal* we publish two articles by workers who have played leading parts in the isolation and testing of this compound. That by Dr. E. Lester Smith gives the story of the work which resulted in its discovery. In the 22 years since Minot and Murphy first discovered the effectiveness of liver therapy in pernicious anaemia there has been a gradual advance in methods of purifying liver extracts, though it is now known that these purified extracts contained less than 1% of the active constituents. This was due to lack of a suitable method of separation from inert material (eventually overcome by partition chromatography), the extremely small quantity of vitamin B_{12} present (less than 1 g. in 4 tons of liver[2]), and the absence of convenient methods of assay. The success of Lester Smith's fractional crystallization depended upon the results of clinical trials of more than 80 samples carried out by Dr. C. C. Ungley, the author of the second paper in this issue. In this type of work the greatest care and patience are needed to avoid false results, and it is to the credit of the clinical workers that they were able to lead the laboratory workers along the correct path.

Dr. Ungley's carefully planned investigation of the treatment of pernicious anaemia by injections of vitamin B_{12} was carried out on 53 cases, the largest series yet published. He took great care to ensure that responses were not due to spontaneous remission or to factors in the diet, and he was able to offset the effect of variation in the initial red-cell count by the use of statistical methods. Having worked out a logical scheme of dosage Ungley is now able to say with greater certainty than any previous worker how much vitamin B_{12} is required to treat patients with pernicious anaemia. It seems that a single dose of 10 μg. produces as good a response, judged by reticulocyte increase or, better, by the rise in the total red-cell count over a period of 15 days, as is usually obtained with ordinary liver extracts. Larger doses give even better results, and the amount required to restore the red cells to 4.5 million or more in 32 cases ranged from 15 to 140 μg. These amounts led also to an increase in white cells and platelets and to clinical recovery. Twenty-one patients have been followed up for six to fifteen months while receiving 10 μg. every two weeks, and only three have not been maintained in an entirely satisfactory state. No fresh neurological symptoms appeared, and those already present improved or at least did not progress. Ungley considers the results of treatment of eight cases of subacute combined degeneration of the cord to be as good as those obtained with liver extract, either crude or refined. This contrasts strongly with the results of folic acid therapy reported recently in this *Journal* by Israëls and Wilkinson,[3] who concluded that folic acid should never be given to patients with subacute combined degeneration of the cord. Ungley suggests a dosage schedule consisting of 40–80 μg. initially, 20 μg. weekly for three months, and 30 μg. every three weeks thereafter for the uncomplicated case of pernicious anaemia, with double these amounts and more frequent administration when neurological symptoms are present.

The use of microbiological methods of assaying vitamin B_{12} activity, developed in the U.S.A. during the work which led to its isolation there, enables the strength of liver extracts to be measured in terms of a pure substance. Dosage will thus cease to be empirical. The isolation of vitamin B_{12} from the metabolism fluid of cultures of *Streptomyces griseus* (used in the manufacture of streptomycin) is referred to by Lester Smith, and commercial production from fermentation liquors is now practicable. The use of the pure vitamin may obviate the reactions which occasionally occur with liver extract and will certainly enable larger amounts of the anti-pernicious-anaemia factor to be administered. Thus the outlook for patients with cord changes may be improved. No doubt, however, further discoveries will soon be made. Already there are known to be

[1] *British Medical Journal*, 1949, **2**, 694.
[2] Smith, E. L., *Nature, Lond.*, 1948, **161**, 638.
[3] *British Medical Journal*, 1949, **2**, 1072.
[4] Spies, T. D., Stone, R. E. Lopez, G. G., Milanes, F., Toca, R. L., and Aramburu, T., *Lancet* 1948, **2**, 519.

two, probably three, active substances in the crystalline fraction, and their relationships and chemical structure are being studied. The part played by folic acid and thymine[4] still remains a mystery. On the clinical side, too, there are many unanswered questions. The nature of the "intrinsic factor" is still unknown. The source of vitamin B_{12}, whether dietary or the result of bacterial synthesis in the gut, is uncertain. There is no satisfactory explanation why some patients develop subacute combined degeneration of the cord when anaemia is only moderate or even absent and other patients with severe anaemia do not develop it, why spontaneous remissions occurred before liver was used in treatment, or why some patients are, or become, refractory to treatment with liver extract. The discovery of vitamin B_{12} has already helped the search for the answer to these and other questions.

THE EYES IN MALNUTRITION

It is not surprising, since the normal eye is a most sensitive and delicately poised optical instrument, that optical abnormalities should frequently occur as an effect of disease or that they should be given prominence when they are a characteristic feature of any particular illness. Besides being a secondary effect of disease, however, eye lesions may sometimes be the first signs of dietary deficiency. In recent years much new knowledge has been gained about nutritional requirements, and many books and papers have been written around clinical and experimental observations on the state of the eyes in various forms of malnutrition. Dr. Hugh Stannus's scholarly and critical essay on "Nutritional Eye Disease,"[1] for which he was recently awarded the Treacher Collins Prize, is therefore to be welcomed as a valuable review of this important subject. In his earlier chapters Stannus assumes that disorders of nutrition may result from senescence, inborn errors of metabolism, endocrine derangements, metabolic diseases, and various congenital deformities, dystrophies, and abiotrophies, and he discusses many pathological conditions, both common and rare, in which the eyes are affected, though it may be questioned whether nutritional factors are concerned in all of them. In his description of the biochemistry and metabolism of the various parts of the eye he points out that the lens is completely isolated from any blood supply and is believed to have its own internal auto-oxidation system, in which ascorbic acid and glutathione, both present in relatively large quantities, may be vitally concerned.

Stannus devotes most space to a discussion of the effect of either primary or secondary deficiencies of individual nutrients on the structure and function of the eyes, with particular emphasis on the effects of deprivation of vitamins. According to present evidence, vitamins A, B_1, C, and riboflavin seem to be more important than others for maintaining the health of the eyes, though Stannus briefly reviews the whole range of vitamins and the general effects of their deficiencies. As examples of the various ways in which nutritional deficiency may affect the eyes the four main lesions which can result from deficiency of vitamin A have special interest. In human beings and in rats avitaminosis A frequently gives rise to xerophthalmia and keratomalacia. These abnormalities are generally regarded as the classical signs of deficiency of the vitamin and frequently cause permanent blindness in Eastern peoples. In rats deficiency of vitamin A during pregnancy often causes ocular defects in the offspring.[2] In dogs deficiency of the vitamin may disorganize bone growth, and stricture of the optic nerve may result from occlusion of its foramen.[3] Deficiency of vitamin A also causes defective dark adaptation: the abnormality in this instance may be traced to a defective formation of visual purple, a photosensitive pigment present in the retinal rods. At least one form of this pigment, if Stannus's view is accepted that a group of pigments is involved, consists of vitamin A in combination with protein. Deficiency of a single vitamin, therefore, may lead to permanent blindness by three distinctly different anatomical routes. A serious functional disturbance also results if the same vitamin is not available to take part in the complicated mechanism of the retina; for this it takes on a form in which it is unknown in any other tissue.

Deficiency of vitamin B_1 causes similar optical lesions in diseases arising in widely different circumstances. Thus Wernicke's encephalopathy,[4] a disease in which sight is affected by lesions in the periventricular grey matter of the brain, with varicose deformities of the blood vessels and petechial haemorrhages, was described long ago in alcoholic patients, and was later considered to be associated with a secondary deficiency of vitamin B_1. Subsequently a very similar picture was observed in the "Chastek paralysis" which afflicted artificially reared silver foxes when they were fed upon raw fish. Research soon indicated that the fish contained a toxic substance capable of inactivating vitamin B_1, which was effective in the treatment of the disease. Finally, Wardener and Lennox[5] noticed a similar syndrome, often fatal, in a large number of prisoners of war at Singapore whom they considered to be suffering from "cerebral beriberi." Thus secondary deficiencies of

[1] Stannus, H. S., "Nutritional Eye Disease." Manuscript copy presented by the author to the library of the British Medical Association.
[2] Warkany, J., and Schraffen-Berger, E., *Proc. Soc. exp. Biol., N.Y.*, 1944, **57**, 49.
[3] Mellanby, E., *J. Physiol.*, 1940–41, **99**, 467.
[4] Wernicke, C., *Lehrbuch der Gehirnkrankheiten*, 1881, **2**, 229, Berlin.
[5] *Lancet*, 1947, **1**, 11.
[6] *Publ Hlth Rep., Wash.*, 1940, **55**, 157.
[7] Burgess, R. C., *Proc. Nutr. Soc.*, 1945, **5**, 116.
[8] Raadt, O. L. E. de, *Thesis*, 1947, Leiden.

vitamin B_1 caused by two different toxic agents, or by prolonged and severe dietary deficiency, all eventually lead to the development of similar syndromes. In riboflavin deficiency there is a heaping up of soddcn epithelium on the palpebral commissures, in common with all orifices of the body, the typical signs having been observed by Stannus in malnourished individuals nearly forty years ago. The patients complain that their eyes itch and burn, and visual acuity is sometimes poor. Stannus, however, disputes the claims originally made by Kruse and Sydenstricker[6] that a deficiency of riboflavin may be diagnosed by slit-lamp examination of the vessels in the limbus, since other factors have to be taken into account. Dr. Stannus concludes his monograph with a comprehensive account of the optical abnormalities which were frequently observed in prisoners of war in the Far East subsisting on diets deficient in both quantity and quality. In these circumstances retrobulbar neuritis was often a prominent symptom, probably associated with riboflavin deficiency.[7] Nystagmus with oto-neurological symptoms was also common and believed to be an early manifestation of pellagra.[8] Pick's visions, or the so-called partial visual vertigo, were another disturbing feature; the patients saw jumbled print when they attempted to read, and sometimes had the impression that their companions left the room by walking through the wall.

VITAMIN E THERAPY

The difficulty of deciding whether vitamin E has any real value in the treatment of human diseases was emphasized by the contradictory opinions expressed at the International Conference on Vitamin E which was held in New York earlier this year and on which we commented at the time.[1] Massive doses of α-tocopherol were claimed by Dr. Evan Shute and others who belong to his school of thought to be effective in the treatment of cardiovascular diseases, chorea, ulcerations, burns, multiple sclerosis, urethral strictures, Dupuytren's contracture, Peyronie's disease of the penis, and even diabetes. Most of these claims, however, were contested by other investigators, who described carefully controlled trials in which they had failed completely to observe any benefit from vitamin-E therapy. In spite of these severe criticisms vitamin E has continued to be widely prescribed in Canada and the U.S.A.

Recent reports have increased doubts about the value of vitamin-E therapy. In the treatment of a small, carefully selected series of cases of angina pectoris Ravin and Katz[2] found that tocopherol was valueless. Bensley and his colleagues[3] were equally unsuccessful in a careful trial of its alleged beneficial effects in diabetes. To offset these disappointments, however, the use of tocopherol in two recent investigations, reported elsewhere in this issue, appears to have achieved a fair measure of success. Dr. G. Russell Thomson (p. 1382) has tested Steinberg's claim that Dupuytren's contracture is influenced favourably by massive doses of vitamin E. Most of his early cases responded well, and complete extension of the fingers was often restored. The vitamin was also beneficial in the later stages of the disease, but to expedite cures the palmar bands were divided by operation. These observations, however, are open to the criticism that no control cases were given placebos. though confirmatory evidence that the vitamin has a plainly recognizable effect on the diseased tissues might perhaps be inferred from the pain which was often experienced in the palmar bands before the contracture began to respond. Dr. H. C. McLaren (p. 1378) has studied the value of tocopherol in preventing flushing, sweating, and insomnia after artificial induction of the menopause by treatment with radium or deep *x* rays or by hysterectomy and oöphorectomy. Temporary relief was obtained in about 60% of his cases. Since the remaining 40% were relieved by stilboestrol, it is clear that tocopherol is less efficient than are oestrogens in preventing flushings, but it has the advantage of seldom causing the resumption of menstruation. Some of the patients were given placebos for a few weeks before their treatment with tocopherol was begun; only one out of eighteen was cured.

The results of these two investigations raise hopes that vitamin E may have real value in the treatment of certain diseases, even if the more extravagant acclamations of its virtues have to be discounted. Animal experiments have left no doubt that the vitamin is essential for most species, and that the lesions which result from its absence are remarkably diverse. Thus its role in maintaining gestation, which led to its discovery some 25 years ago, is only one of the many manifestations of its activity. Other lesions caused by deprivation of this vitamin are muscular dystrophy, brown coloration of the uterus and skeletal muscles, encephalomalacia, exudative diathesis, and dental abnormalities. Animals whose diets are deficient in vitamin E use and store vitamin A inefficiently, and their fat deposits are turned brown when large amounts of cod-liver oil are given. When the diet is deficient also in protein the animals are particularly vulnerable to liver injuries, whether occurring spontaneously or after the administration of chloroform or other toxic substances. The erythrocytes of deficient animals are unduly liable to haemolysis. From the results of animal experiments, therefore, it would not be surprising if deficiency of vitamin E were found to be associated

[1] *British Medical Journal*, 1949, **1**, 949 and 951.
[2] *New Engl. J. Med.*, 1949, **240**, 331.
[3] *Canad. med. Ass. J.*, 1949, **61**, 260.

with several widely different human diseases. But there is still no evidence that concentration of vitamin E in the blood plasma is particularly low in any of the diseases which it is reported to benefit, or that the food eaten by the patients suffering from these diseases has been deficient in the vitamin. The doses claimed to be effective, moreover, are usually greatly in excess of what is thought to be the normal daily requirement. Shute has concluded that tocopherol in large doses has therapeutic effects which are distinct from its physiological effects at normal intakes. Another possibility is that defects in the tissues may increase requirements for tocopherol, so that the amounts normally supplied by the blood may become inadequate.

Perhaps the most regrettable feature of tocopherol therapy, at its present state of development, is its great expense. Thus in McLaren's investigation an average course of treatment consisted of 18.5 g. of tocopherol given over 37 days, and the cost was £7. For other diseases Shute recommends permanent dosing, which means a constant expenditure of over £1 per week. This heavy cost would obviously be justified for a drug clearly proved to prolong life or prevent disablement, but for a remedy whose efficacy is still in doubt the price seems far too high. For the present tocopherol might justifiably be prescribed in Dupuytren's contracture and in cases of menopausal flushings in which the administration of oestrogens is contraindicated. It may perhaps be worth a trial in Buerger's and Peyronie's diseases. Its value in the treatment of more common diseases is in most instances very questionable, and its prescription should await the verdict of carefully organized research.

SPENS AWARDS TO BE CONFIDENTIAL?

The Council of the B.M.A. and the Central Consultants and Specialists Committee have formulated their views on the "Special Distinction Awards" in a statement published in this week's *Supplement*. They have decided that neither body, nor the Regional Consultants Committees, should have a hand in putting forward the names of suitable recipients of the awards. They recommend the Advisory Committee on Merit Awards to form, after consultation with hospital boards, selection committees in each region comprised of "distinguished practitioners of consultant status who are not themselves interested in merit awards (i.e., being already in receipt of the highest award or retired from practice)." The Council and the Consultants Committee have also suggested criteria for assessing merit.

One recommendation calls for comment: "It would be undesirable that any publicity should be given in the lay press to the practitioners who receive awards, but at the same time information regarding the awards should be available to the profession. If this principle is accepted it follows that there should be no publication of lists of recipients even in the medical press." If there is no publication the information cannot be available to the profession. It is recommended that this information shall be available to *part* of the profession—namely, the Joint Committee and its constituent bodies; boards of governors, regional boards, medical committees, and medical advisory committees. "Apart from this the boards should be instructed to regard information relating to awards as confidential." It is not for the *Journal* to criticize this recommendation of the Council of the B.M.A. to the Advisory Committee on Merit Awards. The fact that it has seen fit to make such a recommendation is in itself a comment on the peculiar innovation in our professional life that has been introduced by this method of augmenting consultants' incomes.

These awards have often been described as prizes—even compared to Nobel prizes. Men like to honour those who win prizes and gain professional distinction for merit in their work. If the recommendation of partial secrecy is acted on, then something quite exceptional will have happened in the profession of medicine—and in the history of prizes and awards. The reasons for asking for partial secrecy are no doubt compelling; the fact that the Consultants and Specialists Committee demanded it is proof enough of this. Secrecy is a form of censorship, and if we countenance it ourselves it may be less easy to fight against it if others should attempt to impose it on us.

TRAUMATIC DIABETES INSIPIDUS

Diabetes insipidus has long been recognized as a rare sequel of head injuries.[1-4] Porter and Miller[5] have recently reviewed the subject, basing their observations on 18 cases. The condition was noted in 13 out of 5,000 cases of non-penetrating head injury at the Military Hospital for Head Injuries at Oxford. In all cases the injury was severe as judged by the length of the post-traumatic amnesia, which was less than two days in only one case. The diabetes insipidus was well controlled by posterior pituitary extract in the 14 cases in which it was used: no case resistant to this treatment was encountered. Eleven patients recovered spontaneously within nine months; one was improving satisfactorily after 15 months; and in the other six there was no evidence of recovery at intervals of from 13 months to eight years after the head injury.

A point of special interest in this study is that the appearance of diabetes insipidus may be delayed. It is obviously difficult in patients whom the injury has made stuporose and incontinent to be quite sure when polyuria and polydipsia start, but the authors are confident that in the majority of their patients these symptoms developed from nine to 30 days after injury. This finding is in keeping with experimental diabetes insipidus in dogs,[6] in which there may be a considerable interval after traumatic hypothalamic lesions before diabetes insipidus occurs. If at the time of operation the pitressin-secreting tissue of the pituitary is also removed diabetes insipidus develops immediately, and it is thought that the delay is due to pitressin

1 Fbstein, W., *Dtsch. Arch. klin. Med.*, 1873, **11**, 344.
2 Kahler, O., *Z. Heilk.*, 1886, **7**, 105.
3 Lhermitte, J., and Albessar, *Rev. neurol.*, 1935, **63**, 716.
4 Warkany, J., and Mitchell, A. G., *Amer. J. Dis. Child.*, 1939, **57**, 603
5 *J. Neurol. Neurosurg. Psychiat.*, 1948, **11**, 258.
6 Heinbecker, P., and White H. L., *Amer. J. Physiol.*, 1941, **133**, 582
7 Greene J. L., *Ann. de méd. leg.*, 1938, **18**, 226.
8 Hall, G. W., and Leroy, G. B., *J. Amer. med. Ass.*, 1936, **106**, 431
9 Hendry, J., *Glasgow med. J.*, 1921, **96**, 147.
10 *Bull. Mém. Soc. Chirurgiens, Paris*, 1921, **47**, 685.
11 *Nouv. Iconograph de la Salpétrière*, 1916–18, **28**, 185.
12 *Trans. Amer. neurol. Ass.*, 1939, **65**, 63.

being secreted for a time by the denervated neurohypophysis. A record was kept of the concomitant intracranial damage in these patients; injuries of the optic chiasm, optic nerves, and olfactory nerves were frequent, but in one case only was there undoubted clinical evidence, apart from the onset of diabetes insipidus, of hypothalamic damage. This was a man who developed an adiposo-genital syndrome during the 15 months following his head injury. The adiposo-genital syndrome has been reported by other workers[7 9] as a symptom of hypothalamic damage following head injury, and also narcolepsy.[7 8]

No post-mortem studies could be made in Porter and Miller's series of cases, and, as is so often true in non-penetrating head injuries, the exact location and mechanism of the neurological damage is to some extent speculative. The authors think that the damage was probably in the pituitary stalk, due to stretching when the brain was displaced at the time of injury, and that some patients recover completely because not all the fibres in the stalk are completely severed. They suggest that the relative rarity of other hypothalamic symptoms is due to the early death of most patients who have severe hypothalamic injuries.

Two earlier case reports provide useful information about the site of the injury in traumatic diabetes insipidus. Reverchon and Worms[10] described the post-mortem appearances in a case in which the hypophysis was completely unrecognizable and was reduced to a nodular mass surrounded by a fibrous capsule. Unfortunately no special mention was made of the hypothalamus, presumably because the case was reported at a time when attention was directed to the pituitary rather than the hypothalamus in the pathogenesis of the condition. The case of Maranon and Pintos[11] is more instructive. A boy was accidentally shot by a pistol through the middle of his forehead from a distance of three metres; he did not lose consciousness, felt no pain, and actually went on playing. One month afterwards he developed excessive thirst and polyuria, and 16 months later an adiposo-genital syndrome. He died following an exploratory craniotomy, and at necropsy the bullet was found lying in the floor of the third ventricle with its point in the direction of the pituitary stalk. There was a fibrous capsule around the bullet involving the tissue of the stalk, but there was no evidence of damage to the pituitary. These findings are of particular interest, since they also were described before attention had been directed to the hypothalamus and pituitary stalk; they agree closely with the results of Magoun and Ranson's[12] experimental work on the cause of diabetes insipidus and the importance of the anterior part of the hypothalamus and the fibres running through the pituitary stalk from the supra-optic nuclei to the posterior pituitary.

ERYTHROCYTES IN LIVER DISEASE

The important role of the liver in haemopoiesis has been recognized since the classical work of Minot and Murphy,[1] and much information has since been obtained about disturbances of red-cell formation in patients with hepatic disease. The most frequently recorded deviation from the normal blood picture is an increase in the size of the red cells, the reported incidence of this abnormality varying from 25 to 100%. Much of this variation is probably attributable to differences in methods of observation used by different observers. Quite logically, therefore, Larsen[2] in Oslo, before re-examining the effect of hepatic disease on red-cell size, examined the whole question of the technique of cell measurement and the possible errors therein. The thoroughness with which he has tracked down and exposed sources of error is reminiscent of the meticulous work of the German pathologists in their heyday. The work is in fact but one more example of the leading part Scandinavian workers are playing in medical research. The author has not hesitated to apply every technique at his disposal, and his use of the statistical method is a model of its kind for the exposition of error and the elucidation of significance.

Among the errors which Larsen discusses, and then avoids in his own work, are those due to personal qualities in individual assistants. These are of great psychological interest. For example, some are apt to "draw towards the centre," which makes the frequency distribution curve too high and too narrow, thus greatly reducing the standard deviation. Others show a tendency to "measuring towards whole numbers"; this results in dentate instead of smooth distribution curves. Errors due to optical equipment, photographic recording, colour of the stain, and nature of the light source have all been assessed and so far as possible eliminated. Failure to exclude these sources of error may lead to variation in the mean cell diameter, determined on the same cells, by as much as 1.0 micron. One consolation to the investigator undertaking further work in this field is the conclusion that results of statistical significance are obtainable by measuring only 200 cells in any given case instead of the 500 stipulated by Price Jones.

Using this new and careful technique, Larsen has confirmed the high incidence of macrocytosis in parenchymatous hepatitis. In forty-two of fifty-eight cases a significant increase was observed in the mean cell diameter (M.C.D.) above the normal of 7.79 microns. No increase, however, was found in the mean cell volume, from which it is obvious that the cells are unusually thin. This interesting finding accounts for the difference in incidence of macrocytosis in hepatic disease recorded by different observers, for the results depend upon whether the size of the cell is estimated by the haematocrit or by actual measurement of cell diameters. Of greater interest, however, than the confirmation of increased M.C.D. in hepatitis is the further information obtained about how this occurs. Increase in size could result from peripheral causes in the circulation or central causes in the marrow. Larsen's results prove conclusively that it is the central causes which are of greatest importance. By a modification of a method of statistical analysis introduced by Mogensen[3] he demonstrates that the abnormal frequency-distribution curve of the red cells observed in hepatitis can be resolved into two normal curves—one with a normal M.C.D. of 7.81 microns, the other of 8.56 microns. This

[1] *J. Amer. med. Ass.*, 1926, **87**, 470.
[2] *The Distribution of Red Blood Cell Diameters in Liver Diseases*, 1948, Oslo.
[3] *Studies on the Size of the Red Blood Cells, Especially in Some Anaemias*, 1938, Copenhagen.

implies that during an attack of hepatitis an abnormal generation of red cells is produced possessing a larger M.C.D. and a smaller mean corpuscular thickness but with a normal standard deviation.

These characteristics of the red cells in hepatitis are in marked contrast to those found in untreated pernicious anaemia. Analysis of the red-cell distribution curves shows that the blood cell population in the latter condition consists of at least three abnormal components—namely, a left-hand curve of microcytes, a middle curve corresponding to the large cells found in hepatitis, and a right-hand curve consisting of very large cells—as well as one component with normal blood cells. Most unexpected, however, is the finding that in treated cases of pernicious anaemia the distribution curves are still abnormal. The right-hand curve disappears and the left changes gradually to normal; but the middle curve corresponding to the large cells found in hepatitis apparently persists indefinitely. The cell population in pernicious anaemia is therefore quite different from that in liver disease, but becomes remarkably similar to it after treatment with the anti-pernicious anaemia factor in liver. The question why a generation of unusually large thin cells is produced in cases of hepatitis is not answered by Larsen's work. The most obvious explanation is a deficiency of a factor required for the maturation of macronormoblasts to normocytes. Trial of several nutritional factors suggests that nicotinamide is such a factor.

A further and unexpected result of this work is yet another liver-function test. Measurements of M.C.D. and M.C.V. would appear to be of diagnostic value, since an increase of the former without increase of the latter strongly suggests liver-cell damage, and the further changes in these indices are of prognostic significance.

HOW DOES E.C.T. WORK?

The value of electrically induced convulsions in the treatment of depressive psychoses is generally agreed, but how they benefit the patient is uncertain. Explanations and theories are confusingly numerous. For instance, it has been suggested that there may be an incompatibility between convulsions and schizophrenia. Convulsion treatment was originally based on the alleged absence of schizophrenic psychoses among epileptics. Again, E.C.T. may free the patient of unpleasant memories by causing temporary amnesia, or a depressed patient may subconsciously feel he deserves some punishment for his inadequacy and unworthiness, and so by interpreting the E.C.T. as a kind of penance he achieves a morbid satisfaction. Another suggestion is that the brain subjected to an electric shock may produce a substance beneficial to the psychosis. Cerletti[1] named this hypothetical substance "acroagonin" and claimed that extracts of brains of pigs killed by repeated electrically induced convulsions have a therapeutic effect on depressive psychoses which is much greater than the effect of brain extracts from pigs dying under happier circumstances. Attempts to explain the benefits of E.C.T. as the result of an "indirect" action on the autonomic nervous system are not convincing, for the autonomic system is concerned in most physical happenings and its exact part in them is by no means clear.

Whatever the explanation may be, there is general agreement that it may not be the convulsion but some product thereof which benefits the psychotic patient. Obviously it would be a great advantage to secure the improvement without the convulsion, and for this reason Ashby's[2] attempt to demonstrate a hormonal mechanism behind the benefit derived from E.C.T. deserves serious consideration. It is now believed that as a result of "stress" the pituitary is stimulated (via the hypothalamus) to produce corticotropic hormones. It would therefore be reasonable to expect a change in adrenocortical activity after the stress of E.C.T. Ashby investigated the excretion of cortical steroids in fourteen psychotic patients submitted to E.C.T. and found that in most cases there was a brisk outpouring of both "sugar-active" cortins and "reducing" cortins during the first few days of treatment, but he could demonstrate no change in the rate of excretion of 17-ketosteroids. Great care was taken to avoid errors in this investigation: the collection of urine was checked by creatinine measurements, and the biological assays were first carefully tested for their reliability. Ashby is rightly cautious about the significance of his findings. Granted that E.C.T. alters the excretion of cortical hormones, and also that it improves psychoses, the question remains whether it is the cortical hormones which are the cause of that improvement. Ashby found that the degree of clinical recovery was greatest in the patients whose excretion of adrenal cortical steroids was increased the most, but he admits that the evidence for this was suggestive rather than conclusive. Nevertheless his results are sufficiently convincing to justify further research on similar lines. If E.C.T. works by stimulating the secretion of cortical hormones then it would be reasonable to expect that the direct administration of the necessary hormones would eventually replace the present relatively unpleasant and dangerous method of producing them indirectly.

[1] *Lavori Neuropsichiatrici*, 1947, Rome.
[2] *J. ment. Sci.*, 1949, **95**, 275.

PRESIDENT-ELECT

Sir Henry Cohen has been appointed President-Elect of the British Medical Association in place of Professor T. P. McMurray, who died on November 16. Professor of Medicine in the University of Liverpool—an office to which he was appointed in 1934 at the early age of 34—Sir Henry Cohen has an international reputation in medicine and bears an authority no less distinguished in the fields of medical education and ethics. He has rendered outstanding service to the Association and the profession as chairman of the Medical Curriculum Committee, which issued its report on "The Training of a Doctor" in 1948, and he is now chairman of the Committee on the Postgraduate Education of General Practitioners, whose report will be published early next year. Since 1946 he has been a Crown representative on the General Medical Council, and he was elected vice-chairman of the Central Health Services Council when it was set up last year. Sir Henry was knighted in the New Year's Honours this year.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

DIAGNOSIS AND TREATMENT OF KETOSIS AND HYPOGLYCAEMIA

BY

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KETOSIS

The presence of ketone bodies in the urine should be regarded as the initial stage of a process which, if allowed to progress, may result in diabetic coma. Whenever the urine is found to contain much sugar it should also be tested for diacetic acid, as it is in the early preclinical stage of ketosis that treatment is both simple and effective. Rothera's test with ammonium sulphate, sodium nitroprusside, and strong ammonia should be carried out first. If this is strongly positive, Gerhardt's ferric-chloride test should also be made. Rothera's test is by far the more sensitive, and may therefore be strongly positive when diacetic acid is present in concentrations too small to give a positive result with ferric chloride. An appreciation of this difference between the two tests will enable them to be used to give a rough quantitative idea of the intensity of the ketosis. A positive ferric-chloride test should always be regarded as indicating severe ketosis and the necessity for immediate treatment.

Causes of Ketosis

Ketosis is often present in untreated cases of moderately severe and severe diabetes, its presence being unassociated with any other morbid process. In treated diabetics ketosis may be the result of nothing more than inadequate control of the diabetes, but there is often some complicating factor present which causes an increase in the severity of the disease. This may be an acute infection such as gastro-enteritis, hepatitis, pyelitis, tonsillitis, or pneumonia, or a local condition such as an insulin abscess, carbuncle, or a septic condition of the feet, including gangrene.

Gastro-enteritis rightly heads the list, as it is one of the commonest causes of severe ketosis and diabetic coma. This is because it not only aggravates the diabetes but also produces a state of starvation and dehydration, both of which favour the development of diabetic coma. Added to this, in some cases, is the false assumption that inability to retain food constitutes a reason for withholding insulin, the patient having been taught that an injection of insulin must be followed by food. It is important in this connexion to remember that stopping food and insulin in a severe diabetic is one of the quickest and most certain ways of producing ketosis and diabetic coma. For this reason, if a diabetic receiving insulin is unable to eat his normal diet he should always try to take the carbohydrate portion as milk, alone or with a proprietary milk drink, fruit drinks sweetened with glucose or sugar, bread and milk, toast or biscuits, and the usual dose of insulin. If no food can be retained the patient should take half the usual dose of insulin and get in touch with his doctor.

Sulphonamides, penicillin, or other appropriate treatment should be given without delay in cases of infection, and local collections of pus should be drained whenever this may be done without a general anaesthetic. Major operations on patients with severe ketosis should, if possible, be postponed until the diabetic condition has received appropriate emergency treatment (see below).

Symptoms and Signs of Ketosis

These are anorexia, nausea, vomiting, abdominal pain, shortness of breath, and drowsiness. The only signs are a smell of acetone in the breath, furring of the tongue, and sometimes flushing of the face. All these symptoms and signs may be absent in the presence of a strongly positive Rothera's test, but if this warning is ignored they may develop with alarming rapidity, especially when the patient starts vomiting.

Treatment of Ketosis

The discovery of significant ketonuria indicates the need for insulin therapy or (if the patient is already having insulin) an increase in dosage or some other modification of the existing treatment. In untreated diabetics with moderate ketonuria a single dose of protamine-zinc insulin (P.Z.I.) will often correct the condition, even if it does not control the glycosuria. In severe ketosis, particularly if the ferric-chloride test is positive, the best treatment is the use of two injections of soluble insulin (S.I.), as described in last week's *Journal* (p. 1345).

A third dose may be given before the midday meal if heavy ketonuria persists for more than 48 hours. It is impossible to be dogmatic about dosage, but it is usually safe to start with about 16 to 24 units in the morning and a rather smaller dose in the evening.

When the patient is already taking insulin, treatment will depend on the type of insulin used and the arrangement of doses. For patients receiving a single injection of P.Z.I. the addition of some S.I. before breakfast is often effective, but if this fails to relieve the ketosis a second injection of S.I. may be given before the evening meal.

When a mixed injection of S.I. and P.Z.I. is being taken, the dose of S.I. should be increased by 8 to 12 units, and if ketosis persists an evening dose of 12 to 20 units of S.I should also be given.

Ketosis in diabetics receiving two injections of S.I. is relatively easy to treat by increasing the dose of both injections and, if necessary, adding 12 to 20 units of S.I. before the midday meal. In all cases care should be taken to see that the daily carbohydrate intake does not fall below 150 g.; if possible, 180 to 200 g. should be given. If the patient is disinclined to eat, the protein and fat portions of the diet may be omitted and the carbohydrate given in the semi-solid or fluid forms described above.

Clinical Ketosis or Pre-coma

When symptoms and signs of ketosis are present the ferric-chloride test will usually be found to be positive, and the condition should be considered as a medical emergency. Treatment consists in giving injections of S.I. and carbohydrate feeds at regular intervals, the following method being both simple and convenient.

The patient's urine is tested four-hourly for sugar (by Benedict's test) and for ketone bodies, and after each test an injection of S.I. is given, the dose depending upon the

amount of sugar present in the urine. Thus, for a red or yellow test the dose may be between 20 and 40 units, for a green test with a yellow deposit 12 to 20 units, and for a blue test 0 to 8 units. Dosage will depend on the height of the blood sugar, if this is known, the severity of the diabetes, and the intensity of the ketosis, and the figures given must therefore be regarded as very approximate. Fluid feeds containing 20 g. of carbohydrate should be given after and midway between the insulin injections, and, if dehydration is at all severe and the patient is not vomiting, additional drinks of water or one-fifth normal saline may be taken with advantage. When there is any tendency for feeds to be vomited the stomach should be washed out with a solution of sodium bicarbonate. If this fails to relieve vomiting, fluids must be given intravenously in the manner described below. Although blood-sugar estimations are not essential in this form of treatment, they add greatly to the ease and speed with which ketosis can be corrected. An initial blood sugar is of particular value in helping to assess insulin dosage. The following chart was devised by R. D. Laurence and is convenient for the treatment of diabetics with severe ketosis or in pre-coma :

INSULIN DOSAGE IN PRE-COMA

Test urine four-hourly for sugar and ketones.
Inject S.I. after each test.

Colour after Benedict's test	Order of dosage of S.I.
Red or yellow	20–40 units
Green, yellow deposit	12–20 ,,
Blue	0–8 ,,

Give fluid feeds containing 20 g. of carbohydrate after and midway between injections.

Diabetic Coma : Diagnosis

As already stated, this condition represents the end stage of a process of progressive ketosis and is therefore never sudden in onset. The history, if available, will always be that of increasing malaise with symptoms of uncontrolled diabetes and ketosis extending over a period of days or, at least, many hours. In addition, there is often a history of intercurrent illness such as gastro-enteritis or some other infective process. On examination, the signs are a combination of those of ketosis and dehydration. The former produces acetopnoea, a heavily furred tongue, and the deep abdominal breathing—so-called air hunger—characteristic of diabetic coma. The latter is responsible for the lowered ocular tension, dry tongue and skin, low or falling blood pressure, rapid pulse, and cold extremities which together constitute the clinical picture of peripheral circulatory failure or shock. The urine is loaded with sugar and acetone bodies, and chlorides are absent or reduced. The blood sugar almost always exceeds 300 mg. per 100 ml. and may be over 1 g. per 100 ml. In making a diagnosis of diabetic coma it should always be remembered that this condition very rarely occurs in elderly obese diabetics, and that cerebrovascular accidents are not uncommon in such patients. In the absence of diagnostic signs in the nervous system diabetic coma can be excluded by finding ketone bodies absent from the urine, or present in traces only.

Treatment of Diabetic Coma

Patients in diabetic coma should be admitted to hospital as quickly as possible, as the longer the treatment is delayed the worse the prognosis. The patient should be put into a warm bed and kept warm with an electric blanket. A

EMERGENCY DIABETIC TREATMENT

Diet and Insulin Control by Urine Tests

DIET. Carbohydrate grammes.

10 g. C. in	Glucose :	⅓ oz.
	Sugar :	2 large lumps
	Orange juice :	4 oz.
	Milk :	7 oz.
	Benger's :	2 level teaspoons.
	Horlick's :	2 heaped ,,
	Ovaltine :	2 very full ,,
	Bread measure =	10 g. C. (⅔ oz.)

INSULIN. Test urine for sugar before each dose, passing catheter if necessary.

Give insulin hourly at

If Benedict's test is :	*Units*	*Marks on Syringe*
Red or yellow = + + + sugar.....		
Green with copper deposit = Trace.....		
Blue = 0		

CHART RESULTS

Date	Time	Urine Sugar	Ketones Fe or R	Insulin Given	Carbohydrates Given As	Remarks

general examination should be made, without undue exposure, to exclude any general or local infection, and suitable treatment started without delay.

An injection of 80 to 100 units of S.I. should be given subcutaneously and an intravenous drip set up, if possible into a forearm vein and without cutting down. A catheter specimen of urine should be tested for sugar, ketone bodies, and chlorides, and blood taken for sugar estimation. The stomach should then be washed out with sodium bicarbonate solution. It is convenient to use normal saline for the early treatment of dehydration as it also corrects chloride loss and does not obscure the effect of the initial dose of insulin. The first two litres should be allowed to run in as fast as possible, and if the blood pressure remains very low a third litre may be given in the same way, provided that a careful watch is kept on the bases of the lungs for the onset of pulmonary oedema. Inability to overcome peripheral circulatory failure is the commonest cause of death in diabetic coma, and it is worth while giving 2 pints (1.1 litres) of plasma if saline fails to maintain the blood pressure.

By the time all these things have been done the result of the initial blood-sugar estimation should be known and a decision can be made whether to give more insulin at once or to wait three to four hours for the result of the second blood-sugar test. If the level is very high—over 800 mg. per 100 ml.—a further 80 units or more should be given at once, according to the degree of glycaemia, but for lower levels it is safer to wait and see the effect of the initial dose of insulin. Desperate late cases with a very high blood sugar and an extreme degree of ketosis and dehydration may require many hundreds or even thousands of units of insulin, but they are comparatively rare. The early cases of average severity seldom need more than a few hundred units to remove the ketosis and reduce the blood sugar to a normal level.

There is a tendency at present to give needlessly large and potentially dangerous doses of insulin at very frequent intervals to cases of diabetic coma which could be equally effectively and more safely treated with smaller doses given at intervals of three to four hours. After the second blood-sugar reading has been taken, 4% glucose in 1/5 normal saline should replace normal saline and be given by drip until the patient is conscious and able to take fluids by mouth without vomiting. From this stage onwards the treatment should be the same as that described under "Pre-coma."

Marked tachycardia often persists for several days after the patient has come out of coma, and during this period every care should be taken to throw no unnecessary strain upon the heart. Vitamin B by intramuscular injection in doses of 50 or 100 mg. daily has been advocated, on the assumption that deficiency of this vitamin may be one of the factors responsible for the myocardial weakness.

HYPOGLYCAEMIA

This condition is typically sudden in occurrence, and the patient is well up to the time of onset. The symptoms fall into two main groups. The early symptoms are similar to those produced by an injection of adrenaline, and include pallor, sweating, palpitations, and tremor. The later group are due to failure of oxidation of carbohydrate in nervous tissue, and include higher-centre manifestations such as depression, euphoria, inability to concentrate, deterioration in judgment, and amnesia. There may in addition be central nervous system signs, of which hemiplegia, monoplegia, ataxia, diplopia, and paraesthesiae are the most common. Hunger is a common symptom, and headache, nausea, and even vomiting are sometimes produced by hypoglycaemia, especially when it is due to P.Z.I. A recurrent morning headache relieved by breakfast is always suggestive of P.Z.I. overdosage. Loss of consciousness may be preceded or accompanied by epileptiform fits, and is a late manifestation of hypoglycaemia in all but those rare cases in which the earlier warning symptoms are entirely absent.

Hypoglycaemic coma should always be suspected when a diabetic taking insulin is known to have been in reasonably good health within a few hours of loss of consciousness. A good history will almost always serve to exclude diabetic coma, but a cerebrovascular lesion such as a haemorrhage, embolus, or thrombosis may present more difficulty, especially if the patient is elderly and has arteriosclerosis.

Patients in hypoglycaemic coma are pale, and the skin is moist; ocular tension and blood pressure are unaffected, respiration resembles that of normal sleep, and there is no acetopnoea. Signs in the central nervous system should not be relied upon in diagnosis, for reasons already given, but are more likely to be present in hypoglycaemic than in diabetic coma. The urine may contain sugar if the bladder has not recently been emptied, but if a catheter is passed the next specimen will be found to be sugar-free. Ketone bodies are absent; if they are present as the result of starvation they are insignificant in amount. The diagnosis may be confirmed by estimation of the blood sugar, which is always low and usually less than 60 mg. per 100 ml Treatment should never be postponed to obtain the result of the blood-sugar estimation. The differential diagnosis of hypoglycaemia and cerebrovascular accident is rendered simple in most cases by the rapid response of the former to correct and adequate treatment, after which any signs in the central nervous system rapidly disappear.

There is a definite relationship between the time of onset of hypoglycaemia and the type and dose of insulin injected. Thus, small or moderate doses of S.I. tend to produce their maximum effect three to five hours after injection, and larger doses (of 40 units or more) six to ten hours after injection or later. In patients receiving morning and evening S.I., hypoglycaemia is therefore most likely to occur before lunch or tea, and again at bedtime or during the early part of the night, according to the size of dose injected. As P.Z.I. acts most strongly when the patient is fasting, it is most likely to produce hypoglycaemia during the late night or early hours of the morning. Mixed injections of S.I. and P.Z.I. may cause hypoglycaemia before the midday meal, in the late afternoon, and during the night. Globin insulin in some patients resembles S.I. and produces hypoglycaemia before the midday meal, while in others reactions are more common in the late afternoon. If globin insulin is given before breakfast it rarely causes hypoglycaemia during the night.

Prevention of Hypoglycaemia

The time relation between insulin and hypoglycaemia already described makes it possible to anticipate its onset and prevent it by the use of so-called buffer carbohydrate feeds. These should consist of 10 to 20 g. of carbohydrate. For a patient receiving S.I. they should be given at about 11 a.m. and 11 p.m. If a single morning injection of P.Z.I. is being used the feeds are taken at bedtime, and with a mixed injection of S.I. and P.Z.I. at 11 a.m. and on retiring.

Treatment of Hypoglycaemia

First give sugar, glucose, biscuits, bread, jam, chocolate, or some other food with a high carbohydrate value. All diabetics treated with insulin should carry sugar or glucose, and a card stating the nature of their complaint, their dosage of insulin, and the name of the hospital, clinic, or doctor they attend. Such a card can be obtained from the Diabetic Association. Treated early, while the patient can swallow, hypoglycaemia responds very quickly, but care should be taken to give enough carbohydrate to prevent relapse. Three or four lumps of sugar is usually a suitable amount to start with, but more should be given if there is not obvious improvement in 10 to 15 minutes. When consciousness has been lost and food can therefore no longer be given safely by mouth, one of the following methods should be used.

1. *Intravenous Glucose.*—This is the ideal method. If a 60% solution is available a sufficient amount of glucose can be given with a 20-ml syringe to bring all but the most advanced cases out of coma.

2. *Subcutaneous Adrenaline.*—The injection of 15 minims (0.9 ml.) of 1 in 1,000 solution of adrenaline will raise the blood sugar, produce a return to consciousness, and permit a solution of sugar to be given by mouth.

3. *Stomach Tube.*—This is a safe and good method, and allows a wide choice of carbohydrate food to be made.

The majority of cases of hypoglycaemia recover spontaneously, but some pass into an irreversible state in which they die, and others recover with permanent damage to the brain. It should always be remembered that frequent attacks of hypoglycaemia resemble persistent or recurrent ketosis in so far as they indicate a state of poor stabilization, but, of the two, they are probably the more dangerous. For this reason, whenever there is any doubt about the cause of unconsciousness in a diabetic taking insulin, always give sugar alone first; if the condition is due to hypoglycaemia recovery will result, and if it is due to any other cause, including diabetic coma, no harm will be done.

INTERNATIONAL CONGRESS OF SURGERY

MEETING AT NEW ORLEANS

The 13th Congress of the International Society of Surgery, held in New Orleans from October 10–15, was attended by about 500 participants from some 45 countries. All Europe, save Germany and Russia, sent delegates. As usual, France, Belgium, Spain, and Italy were well represented.

Throughout the week the weather was trying, for it was both hot and humid, with some heavy showers. The main activities were centred about the Roosevelt Hotel, which was the headquarters and is not far away from what might be called the medical centre. The huge Charity Hospital with its 3,000 beds is situated there, with the medical departments of the Tulane and Louisiana Universities adjoining.

Each delegate was presented with a useful handbook carrying portraits of the president and the venerable Professor Rudolph Matas, who is still hale and hearty at 89. Professor Matas, honorary chairman of the local committee, is beloved as the doyen of the profession in the South and the lodestar of all medical and cultural activities in New Orleans. The list of sponsors of the Congress was interesting and informative, for it included the State of Louisiana, the City of New Orleans, the Harbour Commissioners, International House, the Association of Commerce, the Public Services Incorporation, and the Universities of Tulane and the Louisiana State. Our own public bodies might take notice of the interest in the Congress shown outside the surgical world.

The people were well aware of our presence and took a lively interest in us, while newspaper publicity was keen and profuse, not only in New Orleans but in the United States generally. Everyone was kind and helpful, and imbued with a refreshing degree of civic pride. The city is spread over a large area, the wide boulevard Canal Street leading to an extensive residential district. The open canals, such a striking feature of the original city, are now covered and bordered with trees. Drainage and water supply are good, and tropical fevers have been banished since 1905, which year marked the conquest of the "yellow jack" scourge and was a landmark of which the medical faculty has much reason to be proud.

The inaugural function took place on the evening of the first day at 8.30 p.m. This was a formal occasion, graced by the presence of the Hon. Walton Butterworth, an Assistant Secretary of State of the U.S.A.; the Hon. Earl L. Long, Governor of the State of Louisiana; the mayor of the city; the officers of the society; Dr. Sandblom, from Stockholm (representing the delegates); and Lord Webb-Johnson, representing the Royal College of Surgeons.

Dr. Arthur Allen, of Boston, vice-president of the society, presided over the meeting. As there were ten addresses to be made, mainly of a general and semi-political character, it was ten o'clock before Professor Grey Turner, the president of the Congress, was called upon to give his inaugural address. The evening was hot and stuffy, and many in the audience must have already reached the point of weariness, if not exhaustion. During the address the president showed by projection pictures of the presidents since the first congress, which was held in Brussels in 1905. His main theme was the training of the surgeon, but in view of the late hour his address had to be considerably curtailed.

Scientific Work

The scientific work began next day. An operating session at Charity Hospital was held from 7.30 a.m. to noon, and the operations were televised to the ballroom of the Roosevelt Hotel. As the galleries for visitors at the hospital provided small accommodation and the floors of the theatres were occupied by many assistants, most delegates had perforce to be content with the television, which was generally agreed to be satisfactory. The screen was 8 ft. by 5 ft. (2.4 by 1.5 m.); the pictures were not in colour, but came out fairly well. Only the immediate operative field could be seen, so that a grasp of the general topography was difficult. There was a running commentary by the operator relayed from the theatres, with some interpolated remarks which were probably not intended to reach the air. The television of other operating sessions was conducted later, when Professors Alton Ochsner, Rives, and others were the operators.

The scientific discussions began on Tuesday afternoon, when Professor Paolucci, of Rome, gave the opening paper on the surgery of the parathyroid. In the discussion Leriche (Paris), Bastos-Ansart (Barcelona), Parsons (New York), Jung and Fontaine (Strasbourg), Mallet-Guy (Lyons), Manzanilla (Mexico), and others took part. Each opener was allowed 30 to 40 minutes and subsequent speakers only five minutes, and it was remarkable how the exertions of the president in the chair managed to keep the speakers pretty well to this schedule. Another feature of the Congress was the installation of the headphone transmission, which worked well enough to give great hopes for its complete success in the future. By adjusting the apparatus each member of the audience could elect to listen to the speaker in the language employed or to hear a translation into French or Spanish. If interpreters familiar with technical terms are available the rendering is naturally better.

The next session, on the surgery of the pancreas, was opened auspiciously by Professor Ian Aird. He was assisted by an excellent series of lantern slides with captions in French. He dealt mainly with operative procedure and gave a detailed account of the exposure of the organ. In the discussion most aspects of the subject were dealt with by speakers from Mexico, Sweden, Bulgaria, North Africa, France, and the United States.

The meeting on post-operative thrombosis and its sequelae was opened by Alton Ochsner and De Bakey, of New Orleans.

and their remarks were supported by imposing statistics graphically presented on the screen. There was a lively discussion, joined by nearly two dozen speakers representing surgical experience from many parts of Europe as well as America. Three points came out very clearly: (1) that these conditions were still a serious menace in surgical practice; (2) that early rising after operation had not reduced their incidence; and (3) that no one method of treatment was generally agreed on.

Surgery of the pituitary was discussed by Paul Martin, of Brussels, in a masterly contribution that fully covered the subject. Fontaine, of Strasbourg, spoke on the suprarenal glands. He emphasized the prominent part played by his great master Leriche in the development of this branch of surgery. As he warmed to his task the speaker's eloquence increased, and it was obvious that in concluding after a good innings there was still much that he would have liked to say. An international discussion followed his address, but failed to produce any special pronouncement.

The evening session at 7.30 was on the causes of recurrences after operation on the biliary tract. The opening by Demel, of Vienna, was in German, and was characteristically emphatic and thorough. It was a great effort, a *tour de force*, much appreciated by those who understood or who had read the translation thoughtfully provided by the secretariat. Some latitude to the earlier speakers in the discussion gave an opportunity to Lahey, of Boston, Mirizzi, of Cordoba, Mallet-Guy, of Lyons, and Pribram, of New York, to illustrate their remarks by a fine show of lantern slides.

Later in the discussion the president drew attention to the reproach to surgery provided by the large numbers of cases in which injuries to the bile ducts had followed deliberate surgical intervention. He stated emphatically the necessity for constantly stressing the importance of prophylaxis. Lahey, with his large experience to draw upon, condemned all methods of intubation and was in favour of a deliberate search for the distal part of the duct followed by end-to-end anastomosis. He claimed that this plan gave the best results by far. The session came to an end about 11 o'clock, after a large number of speakers had made their contributions.

Experiment in Discussion

Friday and Saturday mornings were allotted to the presentation of a long series of 15-minute papers by the younger American surgeons. This session had been arranged by the United States branch of the International Society as an experiment and to offset the rather senior tendency in the general discussions. Although the communications were often of great interest, 12 papers before luncheon and 12 afterwards was a strain and a concentrated mental effort for the audience. A great variety of subjects were discussed, many in the fields of purely experimental surgery or advanced physiology. Several members agreed with the president, who, while extolling the experiment, suggested that it would have been more useful if there had been fewer presentations, with time for questions and limited discussion. The scientific meeting came to an end about 3 o'clock on Saturday, and brought a strenuous week to a happy conclusion.

Of the social functions, a harbour trip on the first day was a good way of getting visitors and hosts to meet and to break the ice. The evening reception in honour of the president, held at one of the fine country clubs, was a delightful occasion. The closing banquet at the Roosevelt Hotel on Friday night was also a colourful and enjoyable function. The president occupied the chair, and proposed the health of the President of the United States. There was no formal toast list, but several speakers were called upon to unburden themselves of appropriate messages. There was tremendous applause when Professor Matas came to the loudspeaker. Despite his years the choice was justified, for he spoke audibly and interestingly in English, French, Spanish, and Italian.

At the general assembly of the society, which once again was presided over by the mature Professor Verhoogen, several important decisions were made. It was agreed that, with certain precautions, both German and Japanese surgeons should again be received into the society. A committee was appointed to make suggestions on the reorganization of the journal. It was also decided that the next, the 14th, Congress should be held in Paris in October of 1951, and Professor René Leriche was elected president.

On Wednesday morning visits were made to the two schools of medicine, which occupy adjoining premises and carry out their clinical teaching in the adjoining Charity Hospital. At Tulane a special visit was paid to the Matas Library, where an interesting ceremony was carried out in honour of Professor Matas. The president, Professor Grey Turner, told the company something of the work of Matas and how much he was admired and respected in England. He also spoke of the uses of a medical library, and especially urged his younger listeners to follow the example of the doyen by the study of medical history, not only for its interest but as an assistance to their immediate studies and as a guide to the future. At this ceremony the president was presented with a silver plaque to commemorate the occasion, in honour of Professor Matas.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

ANNIVERSARY CELEBRATIONS

The celebrations of the 350th anniversary of the foundation of the Royal Faculty of Physicians and Surgeons began at the end of November. The origins of the Faculty were described by Professor Alstead in a recent issue of the *Journal* (November 26, p. 1223).

On Wednesday, November 23, the honorary librarian of the Faculty, Dr. Archibald L. Goodall, delivered the Finlayson Memorial Lecture. He, too, recalled the foundation of the Faculty by a grant from King James VI to Maister Peter Lowe in November, 1599. The history of Lowe and Robert Hamilton, the co-founder, he traced in detail, and he described the great events in the life of the Faculty.

On Friday, November 25, the Lord Provost and Corporation of the City gave a civic reception. The president of the Faculty, Dr. W. R. Snodgrass, in thanking the Corporation, reminded them of the long association of the Faculty with the town council, which had promised "to hold, have, concur, fortifie and menteine thame and thair successouris . . . in tyme cuming."

On the Saturday an exhibition in the art galleries was opened by the president. It is devoted to the history of medicine, with special reference to Glasgow and the Royal Faculty. This exhibition will remain on view until January 31, 1950. The Royal Faculty attended divine service in Glasgow Cathedral on Sunday, November 27, and afterwards marched in procession to the tomb of Peter Lowe, where a wreath was laid.

Honorary Fellowships

At a brilliant ceremony on Monday the Faculty conferred its honorary fellowship on Lord Moran, P.R.C.P., Sir Cecil P. G. Wakeley, P.R.C.S., Professor Hilda N. Lloyd, P.R.C.O.G., Dr. W. D. D. Small and Mr. Quarry Wood (presidents of sister corporations), Sir Hector Hetherington (principal of the University), Professor E. P. Cathcart, Professor G. B. Fleming, and Mr. R. Barclay Ness. Congratulatory addresses were presented by the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh, the Royal College of Physicians of Edinburgh, and the University of Glasgow. The formal proceedings were followed by a reception.

On Tuesday, November 29, the actual anniversary of the foundation, the commemoration dinner was held. The health of the Royal Faculty was proposed by Sir Hector Hetherington, who made a plea for close co-operation between the Faculty and the University in the training of consultants.

The president, in reply, traced the history of the Faculty and noted that in the last century the State, with good intentions, had made matters more difficult for them. He promised that

in the next 50 years the Faculty would do all in its power to adhere to the principles and spirit of the charter.

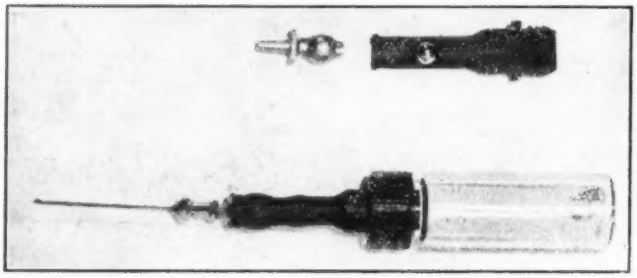
Professor Geoffrey B. Fleming proposed the health of the guests, and there were replies from the Lord Provost and Lord Moran. The former hoped that the Faculty would flourish and expand and that all the younger members of the profession would join it. Lord Moran referred to the position of the Royal Corporations as a bulwark against bureaucracy.

Preparations and Appliances

A SIMPLE VACUUM TUBE FOR COLLECTING BLOOD SAMPLES BY VENEPUNCTURE

Dr. R. H. MALONE, of the Regional Blood Transfusion Service in Sheffield, writes: The vacuum tube described here will be found of great value. It consists of a rubber tube ($\frac{3}{16}$ in.—0.48 cm.—bore), and a hollow rubber bung ($\frac{1}{2}$ in.—1.25 cm.—diameter) combined in one piece, a chromium-plated steel ball-bearing ($\frac{1}{4}$ in.—0.6 cm.—diameter), a male adaptor ($\frac{1}{4}$ in. diameter) slotted at the proximal end, and a glass phial of convenient size (approximately 5, 10, or 20 ml.) with $\frac{1}{2}$-in. neck and screw cap.

For sterilization and to produce a vacuum, assemble the unit, tighten the screw cap, and place in the autoclave for half an hour at 120° C. A test-tube $3\frac{1}{2}$ by $\frac{1}{2}$ in. (8.75 by 1.25 cm.) is inverted on the unit to guard the needle, and on removal of the unit



from the autoclave it is pushed down over the bulge in the rubber tube to form a sterile airtight fitting. Before use inspect the unit to see that the portion of the tube below the ball-bearing is collapsed, indicating a vacuum.

The needle guard is then removed, the needle inserted into the vein, and the rubber tube squeezed at the level of the ball-bearing so that the tubing is pushed slightly on one side. This produces a canal between the inner surface of the tube and the ball-bearing through which the blood is sucked into the vacuum. The needle guard is then replaced.

This unit has the following advantages: (1) A vacuum is automatically produced by sterilizing in the autoclave. (2) Simple inspection shows whether there is a vacuum or not; if the vacuum has been destroyed it can be restored by immersing the unit for 10 minutes in boiling water and then cooling. (3) It can be fitted to any phial with a $\frac{1}{2}$-in. neck and screw cap. (4) It is easily cleaned and reassembled, and can be used many times before the rubber tubing loses its elasticity. (5) Blood samples are taken aseptically. (6) Multiple samples of blood can be taken from the same patient, without removing the needle from the vein, by disconnecting the unit at the adaptor and connecting a new unit. (7) The cost per sample of blood as compared with syringes or "venules" is low.

Any laboratory can assemble its own units once the rubber components have been obtained. The ball-bearings should be chromium-plated or made of stainless steel, since deposits of iron rust cause leakage of air and loss of the vacuum. The adaptor is slotted, because without a slot the ball-bearing, which is forced up by the pressure during autoclaving, seats itself firmly on the end of the adaptor and prevents the escape of air.

The complete unit or the combined rubber tube and bung can be obtained from Messrs. Wm. Freeman and Co., Ltd., Peel Street, Barnsley.

Reports of Societies

MANAGEMENT OF THE GLIOMATA

In the Section of Neurology of the Royal Society of Medicine on December 1, with Mr. JULIAN TAYLOR in the chair, a discussion took place on "Current Trends in the Management of the Gliomata."

Mr. JOE PENNYBACKER discussed in turn the various forms of intracranial gliomata that had come within his experience. Speaking in particular of ependymomata, he said that there was good evidence that these tumours were radio-sensitive, and if surgical measures did not remove them completely it should be possible to deal with any remnants by radiation therapy. He mentioned a case in which an ependymoma had been removed in 1941, the removal being followed by irradiation, and there had been no evidence of return up to the present. The outlook with a medulloblastoma was not favourable, though the literature seemed to show that when such a tumour occurred in adult life the prognosis might be less gloomy. In his series there was only one such case in the favourable group among adults. This patient had remained well for seven years after operation. It seemed possible, however, to approach these tumours with more optimism in the case of adults than in children. Surgery must be accompanied by radiotherapy, and the techniques held out some promise.

Turning to cases of spongioblastoma multiforme, he gave a summary of 89 cases in which a major intervention had been carried out. The operative deaths numbered 14 (16%). Of the survivors, 28 deteriorated within six months, and it was unlikely that any of these were useful survivals; 38 died within 18 months; six within 18–33 months; one at 48 months; and two at 51 months. The procedures undertaken ranged from decompression to complete removal. A rough standard of useful survival was capability for return to work or, in the case of a woman, to household duties. He stressed the unpredictability attending surgery of the gliomas. Surgery alone was powerless in the management of these types of tumours, and the combined efforts of the surgeon and the radiotherapist were essential.

Professor DOROTHY RUSSELL said that her part was to discuss where the pathologist came in in the question of treatment: this, of course, must be in the biopsy diagnosis. The surgeon naturally relied to a great extent upon the accuracy of the pathologist's report; therefore it was useful to discuss the difficulties that arose in the interpretation of the biopsy and the limitations that had to be acknowledged. The main difficulty in a biopsy arose from the admixture of different cytological types and the difference of architecture. On examining certain tumours a curious mingling of highly differentiated types might be found. The pathologist was often forced to use a portmanteau description. The speaker proceeded to review the biopsy material available at her laboratory over a 10-year period: astrocytoma, 119; spongioblastoma multiforme, 129; ependymoma, 30; medulloblastoma, 28; oligodendroglioma, 24. The two first were by far the most numerous types of tumour with which they had to deal. The spongioblastoma multiforme was for the most part derived from the astrocytoma by a process of dedifferentiation or anaplasia. All these cerebral astrocytomas should be viewed with a good deal of suspicion, and it must be insisted that astrocytomas in any part of the brain might behave in the same fashion. Those that occurred as diffuse tumours of the pons and those that occurred in the cerebellum behaved exactly the same. The pontine tumour by reason of its situation, could not be attacked surgically, but in the cerebellum the surgeons could get at the tumour. One met occasionally with cerebellar astrocytomas in which the same changes could be demonstrated. These and many other matters had to be taken into consideration in assessing a biopsy.

Analysis of Results of Treatment

Mr. D. W. C. NORTHFIELD mentioned 58 cases of spongioblastoma multiforme in which a full follow-up had been available. The results were very much as Mr. Pennybacker had

described. Occasionally patients survived for over a year; four had survived for over two years. One patient who was operated on in 1943 was still alive. The tumour in this case was a small one, and the operation was followed by *x*-ray treatment. The patient recovered and returned to work. Four years later there were signs suggestive of recurrence, but these disappeared and no further evidence of deterioration was seen.

The next group consisted of 39 cases of astrocytoma, several of them having long pre-operative histories. In seven of the patients death occurred without any operation or biopsy, and in another seven death followed major craniotomy. The late results appeared unaffected by the operative procedure. There had been a few cases of long survival, up to a maximum of seven useful years. Three patients had lived for over five years; six for over four years. Two patients were still alive. He emphasized the long natural history of some of these tumours.

Of oligodendroglioma there were 15 examples, all subjected to craniotomy. Three died, and the surviving 12 received *x*-ray treatment. One of these was still alive after an apparent total removal eight years ago, but he was handicapped by epilepsy. Another patient had lived seven years after an incomplete removal of the growth.

Only five cases of ependymoma were seen during the period under review, and here the results had been bad. Altogether the treatment of gliomata was a gloomy business. The surgeon was apt to believe, when he removed a compact mass of tumour, that he had taken away a benign growth; but nothing was further from the truth. Astrocytoma was a diffuse infiltrating tumour extending microscopically far beyond the confines of the macroscopically visible growth. The surgeon needed ancillary aid which would inform him at operation whether he had got well beyond the tumour. Any method of showing up tumour tissue would be very helpful. In the surgery of the gliomata, when a tumour happened to be localized the surgeon should endeavour to extirpate it.

An increasing number of gliomata were being treated by radiotherapy. It was difficult to obtain a parallel series of cases with and without irradiation, for no two cases were alike; but they had all seen individual patients in whom, judging by clinical methods, there was no shadow of doubt that irradiation had caused regression. But radiotherapy had its disadvantages and left much to be desired: radio-necrosis was a positive danger.

Sir HUGH CAIRNS said that the general impression to be gathered from the discussion was gloomy, but it seemed important to him to emphasize that the "good" cases came from a group consisting of perhaps twice as many as they had heard about, including cases which had been thought to be gliomata before histological verification was made, and some of these would be benign lesions. With radiographic methods available the needle ought to be able to get right into the region of the tumour almost every time.

No speaker had said very much about the particular situations in the brain in which the tumour was found, but this, of course, very much conditioned the surgery. Mr. Northfield had suggested that they ought to be more radical in the frontal lobe and perhaps in the right occipital lobe. He (Sir Hugh Cairns) did not think there was a case for being more radical, and on the whole he felt that for the more malignant types of glioma the immediate future must be with the radiotherapist. One would like to see some radiotherapist in this country really devote himself to this work. At present the cases were so distributed that no radiotherapist had a really comprehensive experience.

Dr. W. RUSSELL BRAIN said that no doubt modern investigatory methods might miss some tumours of the brain when they were present, but some of these patients who might not have a glioma now were possible candidates for a glioma in the future, and should be followed up, not just written off as cases of cryptogenic epilepsy.

Dr. DENIS WILLIAMS was inclined to think that the electroencephalogram had no value at all in helping towards the exact diagnosis of tumour type. It was only of value in studying what had happened to the brain around the tumour, and the difficulty was that at the time there might be a meningioma, for example, affecting the surrounding brain.

Mr. JULIAN TAYLOR, in winding up the discussion, mentioned the consistency with which the cases seemed to correspond to the clinical picture. When they were looking at cerebral tumours they were not looking at a disease at all, but probably at the results of a disease or of more than one disease; and if that was so, in some of these tumours, as in malignant tumours in other parts of the body, periods of advance, stationary periods, and periods of regression were to be expected.

MEDICAL TREATMENT OF AURAL VERTIGO

A discussion on the medical treatment of aural vertigo took place at a meeting of the Section of Otology of the Royal Society of Medicine on December 2, Mr. GAVIN YOUNG presiding.

Mr. G. H. BATEMAN restricted his paper to the triad of symptoms known as Ménière's disease, which he held to be the vestibular manifestation of a constitutional disorder. He gave the results of a form of treatment used in the ear, nose, and throat department of St. Thomas's Hospital. In this work he had been in collaboration with Dr. J. Kodicek and Mr. L. R. S. Taylor. The treatment which was expounded by Miles Atkinson at the summer meeting of the Section in 1946 was not a perfect one. The patient could not be said to be cured any more than a patient with heart disease could be spoken of as cured when he was controlled by digitalis. Vertigo was caused by a vascular disorder of the small vessels of the labyrinth, resulting in excessive formation of endolymph. The disease might be primary vasodilatation with excessive transudation, or primary vasoconstriction of the arterioles, causing anoxia of the capillaries, which in turn led to excessive transudation through the capillaries when the vasoconstriction passed off. The two groups might be distinguished by a histamine skin test. Cases which gave a negative reaction were treated with nicotinic acid (as a vasodilator). Doses up to 250 mg. t.i.d. had been necessary to relieve the symptoms in some cases. Positive cases were treated by histamine desensitization; 0.05 ml. of a 1:10,000 solution of histamine was injected subcutaneously, and the treatment was continued by doubling the injections on alternate days, increasing the dose by one-half on each occasion. The dose might be increased to about 0.4 ml. of a 1:1,000 solution, but it was rarely possible to maintain the dosage at this rate throughout the course, which lasted about four weeks. By the use of this treatment it had been possible to maintain in active work nine out of ten of the patients who presented themselves.

Mr. L. R. S. TAYLOR added some details of the cases treated at St. Thomas's. Patients who gave a negative reaction to intradermal histamine were given 100 mg. of nicotinic acid three times a day before meals. The patient was told to expect a warm flush 10 minutes later, which would last for 10 minutes. If no flush occurred he was told to chew the tablets before swallowing. After a week he was seen again, and if nothing untoward had occurred 100 mg. t.d.s., a.c., was given for a month. In severe cases intramuscular injections of 50 or 100 mg., once or twice weekly, or even daily at first, might be given. A small maintenance dose must be continued when the symptoms were controlled. Attacks must still be expected, and at the first warning sign—for example, an increase in tinnitus—an intramuscular dose of 50–100 mg. and an extra 100 mg. daily by mouth might be given for a few days. The histamine-positive subjects, after completion of histamine desensitization, had remained well for varying periods up to 18 months, but all had required a second course, and it seemed that a monthly or fortnightly maintenance dose was necessary.

A total of 53 patients had been treated at St. Thomas's, 15 of whom showed a positive histamine skin reaction and 38 a negative one. Vertigo was relieved in 32 and improved in another 20. Tinnitus was relieved in 12 and improved in 22. Both subjective and objective improvement in hearing was noted in 10 cases, the average gain in speech range being about

10 decibels. Headaches, which had been a marked feature in 25 cases, were relieved in 17 and improved in respect of duration and severity in a further six. The cases had been followed up for a period of 18–30 months, and the number of favourable results had far exceeded those following any other non-operative treatment which had been tried.

Mr. I. A. M. MACLEOD gave an account of treatment along similar lines carried out in a series of 50 consecutive cases at Nottingham General Hospital. All the cases were unilateral in type and exhibited the triad of acute vertigo, tinnitus, and deafness in varying severity. Treatment was carried out according to the results obtained from the histamine skin test. The salt used for skin testing and for therapy was histamine acid phosphate.

An initial sensitive reaction was given in 32 cases: 14 were insensitive and the remainder intermediate. The sensitive patients were treated by weekly subcutaneous injections of histamine. The initial dose was 0.1 ml. of 1:10,000 solution of histamine base. This was increased by 0.1 ml. weekly, working up to a concentration of 1:1,000 solution until a reaction was shown by the patient in the form of flushing and headache following injection. This dose was repeated or increased thereafter on three occasions so that four consecutive reactions were produced, and treatment was then stopped. Most patients felt better by the time they had received 0.3 ml. of 1:10,000 solution, as their attacks of vertigo decreased or ceased altogether.

Of the 32 histamine-sensitive cases, 23 had remained free from vertigo since the end of their course (minimum, six months, and maximum, two years eleven months); six cases had relapsed and had further attacks of vertigo, and three cases showed no improvement. The histamine-insensitive group had been treated by nicotinic acid. Initial intramuscular injections of 25–30 mg. were given daily, combined with oral administration of 50–200 mg. Most patients were stabilized on an oral dose only of 50 to 400 mg. daily. Of the 14 cases treated 9 remained free from vertigo; 4 had relapsed, and 1 had not improved. Freedom from vertigo and its accompanying nausea and vomiting had been taken as the criterion of improvement in this series. Improvement in tinnitus and deafness did not take place so frequently.

Mr. C. S. HALLPIKE said that Ménière's disease was in some respects a very satisfactory condition to treat, because the majority of cases did well with little more than a moderate degree of sedation with phenobarbitone, and patients who did not do well on this easy treatment might be referred for the more specialized chemical methods, and again a proportion of them did well. What was unsatisfactory was the rationale of the special treatment, such as histamine therapy. It was sometimes stated that Ménière's disease was an allergic condition, but the manifestations of allergy were multiple, and that did not apply in Ménière's disease. Again, these manifestations of allergy appeared early in life, whereas Ménière's disease appeared later. Finally, there was family history in allergy, which was not seen in Ménière's disease.

With regard to skin tests, they had been told that the cases sensitive to histamine on skin test were the cases in which histamine should be given, and that nicotinic acid should be administered in the insensitive cases. But in his experience, if patients were negative to histamine there was not the slightest reason why histamine should not be given, and vice versa. Histamine and nicotinic acid were chemically quite different, but they had this in common, that they produced an increased vascularity, possibly in the labyrinth, and it did not seem to matter very much which was given. He hoped that more work would be done in investigating the circulation of the fluids in the internal ear.

Mr. I. SIMSON HALL said that each of the various systems of treatment claimed a considerable proportion of successes. The difficulty was to assess the value of each treatment as it was introduced. In an attempt to assess the progress in medical treatment he had studied the medical failures—in other words, the cases referred for operative treatment. In a series of 150 to 200 cases a few years ago he discovered that 20% had been so referred, and in a later series 15%, so that it seemed some advance could be claimed for the new methods.

Mr. GILROY GLASS said that in watching the results, especially those of Mr. Macleod, he had been impressed by the sense of well-being and confidence of the patients. He referred to two cases, alarming at the time but interesting in retrospect. By an error in dispensing a batch of histamine was made up to 1:10 instead of 1:10,000, and two patients received the injection. Both became unconscious, with severe shock, but both recovered. The point of interest was that neither of them had had any vertigo since. Both the patients had been extremely deaf, but on regaining consciousness both had normal hearing, which was maintained in one case for six months and in the other for one month. It was not an experiment to be repeated, but the fact remained that something happened which restored their hearing, at least temporarily.

Mr. TERENCE CAWTHORNE said he had found that, whatever medical treatment was advised, about 50% of patients seemed to be benefited, and if one carried on from one medical treatment to another medical treatment a further 25% might be put in the satisfactory group, leaving about 25% in which more drastic surgical treatment might be required. He had been impressed by the fluctuation of the hearing in hydrops of the labyrinth. One day the hearing would be down, particularly in the dense tones, and another day it would be up.

Mr. H. V. FORSTER mentioned certain compounds which were being tried out in treatment in the United States, and Dr. M. G. GOOD described certain cases of vertigo not dependent on the ear but related to a condition of idiopathic myalgia. Mr. BATEMAN, in reply, said that he did not altogether agree with Mr. Hallpike that most of these patients could be relieved by sedation. He also disagreed with him when he suggested that it did not matter whether the two groups were differentiated by skin-testing or not. If one started therapy without doing a histamine skin test one would be able to predict with great accuracy from the results what the skin test would have shown

Nova et Vetera

OSLER REDIVIVUS

A Year with Osler: 1896–1897. Notes taken at his Clinics in The Johns Hopkins Hospital. By Joseph H. Pratt. (Pp. xxi + 209. $4.) Baltimore: The Johns Hopkins Press. 1949.

This book is an interesting and valuable addition to Osleriana, appropriately published in the centenary year of Osler's birth. It opens with an attractive introduction and preface, but the bulk of the text is a reproduction of notes made over fifty years ago, when the author was a pupil of Osler at the Johns Hopkins Medical School. Osler spoke slowly enough for his statements to be taken down verbatim—"his students cherished his words"—and one of his pupils has now reproduced them for transmission to others.

Such *pietas* is as praiseworthy as the accurate taking-down of some sixty thousand words or more during a single year is remarkable. The would-be reader will ask, Is there value to-day in this detailed, half-century-old record of a clinical teaching session? Will he find it more than an interesting historical document illustrating an era that is now long past, never to return? The answer is, without any doubt, that these notes have been justifiably preserved and published for the benefit of present-day practitioners and teachers of medicine, and that it is impossible to read any page without being stimulated. In particular, the teacher will benefit by the detailed demonstration of a master's way of instructing the young student. But all will learn from the book, and the amount learned will be far from small.

As Dr. Pratt himself writes, "Although these clinical lectures and demonstrations were given fifty years ago, they possess their original freshness in large measure"; and "they show how much can be learned at the bedside by the inquiring mind, the seeing eye, and the trained hand, even without the aid of modern laboratory methods."

K. J. FRANKLIN.

Correspondence

Erysipeloid

SIR,—I was interested in the medical memorandum by Dr. R. A. Bush (October 29, p. 964) and I agree that most cases of erysipeloid are penicillin-sensitive, though during the past few months I have seen two cases which have dragged on for a month or so in spite of adequate doses. I do not agree with the statement that the disease is by no means common. I believe it is more correct to say that it is by no means commonly recognized. At a recent examination for a higher surgical diploma I found that only about one candidate in ten was familiar with the condition.

Erysipeloid is more common in certain localities, and is seasonal—June to October being the optimum months. The reddish-purple area on the hand, which follows a prick by a fish-scale or poultry bone, is very typical. Untreated, this intradermal, *not* subcutaneous, inflammation slowly extends over the adjacent palm or fingers and subsides in from four to six weeks, during which period disability results from itching and stiffness. Regional lymph nodes are occasionally enlarged, probably as a result of the initial skin puncture. I have never seen lymphangitis as described by Dr. Bush.

It is important that this disease should be recognized, both from the point of treatment and maltreatment. The majority of cases respond to penicillin but are resistant to sulphonamides, and surgery is contraindicated—in spite of which I have seen two cases which were incised as indolent whitlows. It is interesting to recall that erysipeloid was described as long ago as 1873 by Morrant Baker, who termed it erythema serpens, and it is now commonly referred to as "fish-handler's disease."—I am, etc.,

London, W.1. R. J. MCNEILL LOVE.

SIR,—Mr. Thomas G. Lowden has made several observations on erysipeloid (November 26, p. 1231) and I am prompted to add my comments on this interesting and often undiagnosed condition, since I treated a fairly large number of cases during a period of 18 months at the Royal Northern Hospital. I would agree that the incidence is in the region of 1% of septic hands seen, that the cases vary in severity, and that the diagnosis is of necessity made clinically, as incision is not required and thus no material is available for pathological study.

"Untreated" cases—i.e., those patients who have only attended for treatment after self-medication with poultices, etc., for several weeks—do not resolve readily in spite of penicillin, taking 2–3 weeks further to clear (i.e., as long as 5–6 weeks from the original date of onset). The condition sometimes spreads slowly on to the hand but is often surprisingly stationary. Although the majority of cases respond to penicillin (250,000 units b.d. for seven days), the response is often slow, and there are a number of cases that do not respond at all but tend to linger on for weeks like the "untreated" cases. These may have not come for treatment until the second week, but early cases too may react in this way. Sulphonamides appear to be entirely ineffective, as shown by cases referred by general practitioners who have tried sulphonamides without success, and by personal clinical trial.

The commonest cause appears to be a minor prick with a fish, meat, or rabbit bone, but pricks with a variety of sharp objects have been seen to cause this condition. I have also seen one case which followed a small burn of the finger, there being no history of any obvious source of contamination. The burn had healed before the patient attended hospital, so there was no opportunity of isolating the organism, but clinically the appearance was quite typical. For some reason the disease appears to have a seasonal incidence, and I have noticed a very definite increase in spring and autumn. I have been told that the disease has a definite topographical distribution, and I would be very interested to hear of its incidence in other parts of the country, in order that this contention may be proved or disproved.—I am, etc.,

London, N.12. CYRIL BORODA.

Lymphoid Hyperplasia and Rheumatoid Arthritis

SIR,—Professor Hans Selye (November 19, p. 1129) discusses possible reasons for the favourable modification of "formalin arthritis" by ACTH, "cortisone," the "alarm reaction," and the worsening effect of LAP and DCA. He suggests that the inhibitory action of ACTH and cortisone may be due to their antihistaminic or anti-hyaluronidase properties.

For some time past I have felt that the lymph-gland enlargement found in rheumatoid arthritis (and some cases of "fibrositis") might be an important factor in the production of the disease, rather than secondary to chronic inflammation in the joints as was formerly believed. Selye's paper on the general-adaptation syndrome[1] encouraged me to pursue this hypothesis, particularly as it lent some support for a basic psychogenic aetiology which I believe to be present in many cases. It is known that the synovial cavities of joints are at least in part drained by lymphatics,[2] and Indian ink injected into these spaces may be found very soon in the appropriate lymph nodes. Professor E. W. Walls and I[3] have recently worked on lymphograms obtained by putting "thorotrast" into the synovial cavities of cadavers and moving the joint concerned. This fills the lymph channels and outlines the nodes in a few minutes. My object has been to gain some idea of the normal, to compare with cases which have previously suffered from rheumatoid arthritis. The snags will be obvious, and the scope of the work has been limited to the cadaver owing to our unwillingness to put thorotrast into the joints of living subjects, though this has been done abroad.

Now the photographs (Fig. 7, p. 1133) and description of what happened to the lymph nodes in Professor Selye's experiments have prompted me to put forward tentatively an alternative mechanical theory—that the changes in the joints are due to lymphatic oedema caused by a partial obstruction by lymphoid hyperplasia. In the experiment referred to the rat's glands are small under the influence of ACTH, and the deep staining shows that absorption of ink was rapid. When the glands were hyperplastic from LAP little ink had reached them. Applying the hypothesis to the aetiology of "formalin arthritis," formalin solution is irritant and is probably dealt with subcutaneously by the lymphatic system. It may well be that the system becomes overloaded or damaged, thereby rendering the mild and uncertain "arthritis-producing" property of DCA and LAP more clear-cut. The intensity of local skin reaction could also depend on the speed of removal of formalin.

Finally, Selye's unexpected finding in his rat experiments of main involvement of the ankle-joint, though it was some way from the site of injection, is also capable of explanation by mechanical block of lymphatics. Clinical observation, too, shows that it is the peripheral joints that are mainly affected in rheumatoid arthritis, and perhaps those in which the periarticular tissue is lax are affected most—e.g., proximal interphalangeal points, as opposed to distal interphalangeal. It should not be difficult, given facilities for animal work, to show whether lymphoid hyperplasia can in itself impede lymph drainage.—I am, etc.,

Ipswich, Suffolk. J. W. PAULLEY.

REFERENCES

1 *J. clin. Endocrinol.*, 1946, **6**, 117.
2 Davies, D. V., *J. Anat., Lond.*, 1946, **80**, 21.
3 Ibid., in the press.

Autotransplantation of Joint Capsule

SIR,—With reference to your annotation (November 26, p. 1221) on this subject, it may be of interest to note that in 1938 we trephined a small controlled series of cases of rheumatoid disease and osteoarthritis at the Royal National Hospital for Rheumatic Diseases, Bath.[1] In the rheumatoid cases no significant improvement was noted, but in those suffering from osteoarthritis there was some relief from the bone pain certain patients experience at night. We felt that some reduction of tension might be the explanation of this improvement in symptoms.—I am, etc.,

Bath. G. D. KERSLEY.

REFERENCE

1 *Reports on Rheumatic Diseases*, 1938, **4**, 68.

Dermatitis and Stomatitis due to Streptomycin

SIR,—I read with interest the article by Dr. R. A. Pallister on dermatitis and stomatitis during streptomycin treatment (December 3, p. 1271) and wish to state that I have seen a similar syndrome in an imbecile child aged 12 years, who also exhibits tuberose sclerosis and whom I had treated for chronic pyelitis with streptomycin.

I started treatment on October 27, 1949, with one gramme of streptomycin daily in divided doses. On October 28 the temperature dropped to normal and on the 30th the urine was much clearer and temperature was normal. On October 31 the temperature rose to 100° F. (37.8° C.). On November 1 the temperature was 100.4° F. (38° C.). The patient was extremely restless and appeared to be complaining of his throat. On November 2 the temperature was 100.2° F. (37.9° C.). The patient was very restless, scratching his abdomen and trunk. His lips were red and sore and the mucous membrane of the mouth was inflamed and sore. Streptomycin was continued. On November 3 the patient, when examined, was found to have a mild stomatitis and later in the day developed a well-marked generalized erythematous rash which was marked on face, trunk, and limbs. The palms and soles were clean. On November 4 the rash and stomatitis were more marked, and I diagnosed the condition as due to sensitivity of the patient to streptomycin, a total of 9.25 g. having been given. I stopped the streptomycin treatment on November 4 and ordered calamine lotion to be applied to the rash, which appeared to be extremely itchy, and "benadryl" tablets (50 mg.) to be taken three times a day. The mouth was treated by mouth washes and gentian violet. On November 5 the patient appeared to be slightly better (temperature normal). On November 6 the rash appeared to be fading and the stomatitis was clearing up (temperature still normal). On November 7 the rash was gone and the stomatitis was much better. A vitamin preparation was prescribed. On November 9 the rash and stomatitis had cleared up. Examination of the urine showed the chronic pyelitis to have cleared up also.

The symptoms of this patient were similar to those described by Dr. Pallister as the symptoms of sensitivity to streptomycin—i.e., fever, stomatitis, and rash. In this case the patient reacted to benadryl. I do not think that there is any doubt that the symptoms were due to streptomycin.

I wish to thank Dr. D. J. Rose for his advice and permission to write up this case.

—I am, etc.,

Brockhall, Blackburn, Lancs P. O. O'REILLY.

The G.P. and E.C.T.

SIR,—The correspondence on E.C.T. emphasizes the great difficulty in selecting the right cases for it if one wishes also to reject unsuitable ones. It appears that the criteria to some extent cut across the ordinary diagnostic categories, and it is, of course, inherently likely that they should, since the classification was not designed with E.C.T. in mind. While we may agree in principle that the G.P. can often provide valuable information on the subsequent career of the patient, it will be quite useless if the psychiatrist does not happen to have noted those features of the patient and his environment which are really critical. They may indeed be so subtle as inevitably to escape notice unless specially looked for.

In a case like this, where only a small part of the theoretically available information can, in practice, be extracted, it is necessary to make an intelligent guess. I suggest that a consideration of the nature of a treatment such as E.C.T. *vis-à-vis* the nature of the disease might aid in this direction. How, in short, might such a treatment be expected to benefit such a disorder? In the first place neurosis has, as the statisticians say, many degrees of freedom, while the treatment has very few. We may speak of neurosis as a failure of integration, a maladaptation, a confusion, or many other things. The point here is that every respectable neurosis is a case of not one or two, but a large number of things being wrong more or less independently. To say that they are wrong independently does not conflict with the fact that we can often see how one thing has led to another to make the patient what he is to-day; the environmental story is an integral part of the causal chain, and it might have unfolded far otherwise than it did.

Now E.C.T. in common with suggestion, drugs, psychosurgery, and environmental adjustment cannot of itself put right more than a few things that are independently wrong. The reason is simply that it is not variable in more than a few independent ways. (Of course it might be in theory; there is an enormous number of distinguishable combinations of current, duration, etc., but it will be agreed that in practice the choice is made from quite a small number.) In other words the treatment cannot be exactly matched to the structure of the neurotic personality. Indeed, no known treatment can, although deep analysis may be said to be an attempt, as far as is practicable.

Nevertheless these relatively non-variable procedures do from time to time result in what seems to be permanent cures; and occasionally so-called spontaneous cures occur. The only way we can account for these happy events is on the supposition that the treatment or, in the latter case, a fortunate concatenation of circumstances has, so to say, "started something." The actual cure must be attributed to the psychological environment continuing to "play up" in such a way and for such a time as to allow the psyche to settle down after the disturbance in a new, and better, stable equilibrium. Clearly in some cases it will have to play up in such a manner so specific and unlikely as to be beyond hoping for. Then, or whenever it fails to play up, we must expect the "brittle mask of cheerfulness," as Dr. D. M. O'Connor (October 29, p. 984) aptly calls it, to crack.

The general criterion of selection, therefore, is whether the temporary disturbance will enable the patient to learn what he has to learn from the best obtainable subsequent environment (which may include a psychotherapist). It is a strategical problem in which diagnostic categories can play only a limited, though not unimportant, part and in which no amount of care will ensure success every time.—I am, etc.,

Cambridge. W. E. HICK.

SIR,—I feel that Dr. Donald M. O'Connor (October 29, p. 984) has raised an important issue by his letter on E.C.T. and one which should not be dismissed casually. Innumerable papers are published giving statistics of cure by various physical treatments—E.C.T., insulin (modified or deep), prefrontal leucotomy, narco-analysis, and so on—but the degree of cure is assessed by the physician who has given the treatment and not by the G.P. who sees the patient every day. It is obvious that anyone using a therapy for which he has a strong enthusiasm will consciously or unconsciously be prejudiced in its favour. The only person who can give one valuable information is the G.P., and he is never quoted in statistics.

In my opinion physical treatments are useful, but only in a very limited way. For example, E.C.T. will produce excellent results in certain cases, as in menopausal depressions, but this does not mean that all depressions should be put through a "sausage-machine" routine as is so often the case. I know, for instance, of a young man who was homosexual and depressed as a result. He was given E.C.T. without even an inquiry regarding any sort of cause for his condition. In the same way I feel that insulin therapy produces occasional cures, but these are not nearly so frequent as its exponents would have us believe. At almost every one of my out-patient sessions I encounter cases of schizophrenia which have had insulin therapy without any beneficial effect and have even been given E.C.T. (which the statistics of the New York State Hospital show is harmful for such cases). I need not describe the failures from prefrontal leucotomy—they are all too evident. The enthusiasts give us a high rate of cure for such treatments, but what does the G.P. think of them?

There is a strong urge from official bodies that patients should be treated rapidly and inexpensively, so that statistics of cures may be produced and good results may be quoted. I have even heard of one medical superintendent in a mental hospital who discharged all of his doubtful cases just before the time to assess statistics of cure. He could thus show a high recovery rate—although most of those discharged returned the week after. Careful studies in America show that the best results come from clinics where patients are treated as people with anxieties and troubles and not as machines which need a

good jolt to get them going again. I would therefore plead most strongly that we need the observation of the G.P., who does regard his patients as human beings, to correct the mechanistic vision of the enthusiasts for physical regimes.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

SIR,—Dr. Donald M. O'Connor (October 29, p. 984, and December 3, p. 1297) is very right to stress the intense fear and dread expressed by a considerable number of patients. I have frequently discussed this with them when back in their own homes and secure. Most say they cannot say what it is they fear—there is no pain, no unpleasantness, and yet they cannot face it again. Many say they have heard the previous patient cry out and the sound has frozen them with fear—I even had one patient who saw her predecessor being wheeled out unconscious. I have, like Dr. O'Connor, found a curious lack of appreciation of this phenomenon among institutional psychiatrists.

As to sequelae, the patients, the relatives, and many doctors are very distressed at the amnesia and confusion so many show on returning home. In very few cases does it last for more than a few weeks. One of my cases developed a full-blown hemiplegia which cleared up in a week or two. Sometimes there is complaint of backache or soreness of joints (hip, knee, ankle). I think this is why the hysterical type does so badly—they get a displacement of their symptoms, they do not lose them.

In reply to Dr. D. N. Hardcastle (December 3, p. 1297) I think a very great deal of information would be gained by the psychiatrist if the mental hospitals had a really good follow-up team. Here in Bristol, for instance, if a patient has had any form of radium or contact *x*-ray treatment, one receives a regular and standard form of inquiry year after year. I do not think I have ever received a similar query about a psychiatric case, and only an occasional one on a surgical or medical case.—I am, etc.,

Bristol. J. L. FAULL.

Medical Administrators

SIR,—Dr. John Sleigh (November 19, p. 1180) has properly understood my meaning, which, briefly, is that medical men and women should primarily be engaged in the practice of their profession so as to avoid waste of medical man-power at this critical time. Training for administrative work is far less arduous and time-consuming than it is for medicine, calls for relatively few technical qualifications, and is largely intuitive. A layman can do the work if he has common sense, tact, some knowledge of house planning, essential services, housekeeping, and the ability to get along with other people. By attending the meetings of the medical and lay committees he and they are in touch with all requirements and have technical advice available.

Any well-designed administration with a minimum of staff runs by itself. One such that I took over at short notice and ran for seven weeks was, I believe, improved by the change. The so-called work took me from 9 a.m. to 9.15 a.m., and I attended from 6 p.m. to 6.30 p.m. to receive complaints, look over and sign letters, etc. My round was made between these times. Motto—keep the staff small and have an occasional meeting.

The contrast between the health of the community when I was a student and now, especially among the young, is astonishing. In those days rickets, anaemia, and skin diseases were rife, rheumatic fever and venereal disease common, and undernutrition the rule. The children were pale and wan. To-day, with sun-balconied flats, scientifically adjusted food, cleanliness, better school premises, and better feeding, the children are fine and healthy. All this is primarily due to lay planning with medical and scientific advice and to the prevention of infection.

In former times a doctor with the D.P.H. was regarded as a sort of cross between one who wished to avoid practice and a plumber. Being of a mechanical turn and interested in science, building lay-outs, sewage farms, and the like, I nearly went in for it. To-day the bacteriology alone would be far beyond me.

By all means have medical superintendents, but let them also practise as consultants in their own institutions and do a full day's clinical work. Many do, and sometimes dislike the administrative duties that have been thrust upon them.—I am, etc.,

London, W.1. G. H. COLT.

Use and Abuse of Vitamins

SIR,—Professor L. S. P. Davidson (November 5, p. 1036) points out that frank deficiency diseases are rarely encountered in Great Britain to-day. In this connexion I should like to mention a case of mine, a girl of 18 years, whose skin would not stand sunlight. She was seen by an experienced consultant physician and by a leading dermatologist, neither of whom accepted my diagnosis of pellagra. The only suggestion made as to treatment was to carry a sunshade. In the end she was persuaded to eat ½ oz. (14 g.) of raw yeast daily, and when last seen was quite well.

It may be argued that this is a very unusual case, but most doctors must have come across cases of herpes labialis. This condition arises from nicotinamide deficiency and can be quickly relieved by giving nicotinic acid in suitable doses. Herpes simplex can also be produced at will, for instance, by giving a course of sulphapyridine followed by an artificial pyrexia from T.A.B. vaccine.[1] I will not say anything about surgical incisions failing to heal from lack of vitamin C, as this particular difficulty seems to be getting less troublesome.

The answer seems to be that a frank deficiency to one doctor may be a sealed mystery to another. I well remember being told as a student in the pharmacology class that "cod-liver oil was only useful as a source of calories," and must confess to a certain distrust of academic medicine ever since.—I am, etc.,

Shipley, Yorks. HENRY S. RUSSELL.

REFERENCE

1 Van Rooyen, C. E., Rhodes, A. J., and Ewing, A. C., *British Medical Journal*, 1941, **2**, 298.

Menstrual Histories

SIR,—The importance of accurate information concerning the menstrual functions of women has long been recognized by physicians, surgeons, obstetricians, and gynaecologists alike. The uncertainty and indifference to accuracy exhibited by the average woman (even among the better-educated classes) in describing these functions are proverbial. The time wasted by the medical profession throughout the world in arriving at accurate data when trying to get a menstrual history must be phenomenal.

After 22 years' experience in hospital and private practice of this unsatisfactory state of affairs, I should like to put forward a solution to this problem. For the past six years I have consistently handed to nearly every woman between 15 and 50 years old under my care a card which I devised for the purpose and which I have found invaluable in my work. The headings on the card, which is printed on both sides, are reproduced below.

DATE NAME AGE PARA: SMWSDR 12.

TEL.: ADDRESS MISCARRIAGES: OCCUPATION

Date of ONSET (a.m. or p.m. and Day of Week)	Duration Profuse, Normal, or Scanty	Pain: (Present or Absent and When)	Number of Days Since Previous ONSET	Changes in Health or Routine of Life	Remarks (e.g., Emotional Upsets) and Treatment (if any)

The patient needs only to make an entry approximately once a month on the card, which is designed to last in most cases for one year. When complete it can be returned to the medical adviser to be filed with his records of the case. The ready

and willing co-operation of the average patient in this simple method I have found most gratifying, and the importance of the information thus obtained (with the minimum of effort on the part of the doctor) is great.

The objection might be raised (as it has been in some quarters) that it is undesirable to let women, particularly certain introspective types, pay so much attention to what should be considered a normal physiological function. But my experience over many years is that it does not encourage preoccupation with the "periods" and has no undesirable psychological effect. Details have to be recorded only about once a month, and the card merely takes the place of the private jottings in the patient's diary or calendar.

SMWSDR 12 at the top of the card stands for single, married, widow, separated, divorced, remarried, once, twice, etc.

—I am, etc.,

London, W.5. L. CARLYLE LYON.

ACTH and Colchicum in Gout

SIR,—It would seem that the only hope of making wide clinical use of the anti-arthritic effects of "cortisone" and ACTH lies in the development of analogues which would be reasonably easy to manufacture. To this end research to ascertain the chemical mechanism whereby the drugs work is under way.

Unfortunately the rate at which this work can progress is also greatly restricted by shortage of the drugs, especially in Britain. A possible line of approach to the problem utilizing freely available material has occurred to me. According to Selye[1] gout is as much a "disease of adaptation" to stress as arthritis. Might it not be worth while then to investigate the mechanism of the specificity of colchicum against gout? It seems that nothing is known about how this agent produces its effect. In fact, only recently has the chemical structure of its main ingredient, colchicine, been investigated.[2]

When injected into patients with gouty arthritis, ACTH increases uric acid excretion with a concomitant fall in serum uric acid level.[3] Presumably colchicum acts by producing the same effect. Exact knowledge of how colchicum works might therefore provide useful clues to the development of the required analogues.—I am, etc.,

London, E.C.4. CHAPMAN PINCHER.

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2 Tarbell, D. S., *Science*, 1949, **110**, 446.
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Pruritus Vulvae

SIR,—Professor T. N. A. Jeffcoate in his comprehensive paper on pruritus vulvae (November 26, p. 1196) rightly stresses that the general practitioner, the gynaecologist, and the dermatologist tend to see different aspects of the problem. The dermatologist is mainly concerned with those persistent cases that remain after the elimination of those that are more amenable or due to internal gynaecological conditions. He finds that one simple cause is rarely responsible but that more often these cases result from blends and combinations of the "big seven" of contact irritants, emotional, endocrine, infective, metabolic, and nutritional disorders and skin diseases.

A good history is the *sine qua non* for accurate diagnosis, and an illuminated text, *Qui bene interrogat, bene diagnoscit*, would make a good reminder if suspended over the examination couch. A full psycho-physical assessment is necessary, and the unmasking of one cause must not lead to relaxation of the search for others.

The physical signs may indicate the cause or only reveal the added effects of physical, chemical, or microbic damage, which vary both according to the patient's type of skin reaction and the nature of the irritant. These secondary physical signs include lichenification, excoriation, furunculosis, impetigo, infective dermatitis, and eczematous dermatitis. Infection suggests a greater probability that diabetes may be present, but it also arises from nutritional deficiency or from scratching. Even if psoriasis is the local manifestation it must be borne in mind that this disorder does not usually itch and, further, that its presence in the flexures may show the psoriatic's skin reaction to scratching rather than the cause of the pruritus. For this reason the investigation of psoriasis of the vulva must be on similar lines to other obscure cases of pruritus vulvae.

Physical signs due to nutritional deficiency include seborrhoeic eruptions, dermatitis confined to the labia majora, leucoplakia, and intertriginous (monilial) dermatitis. The latter most commonly occurs with diabetes or pregnancy, and in other cases avitaminosis (usually conditioned) must be considered, because monilia may be found on the skin of many women without pruritus as a harmless skin contaminant. Avitaminosis may arise from achlorhydria, gastro-intestinal disorders, fads in dieting, or from insufficient food in elderly women, possibly edentulous, living alone. Drug intoxications, as from gold and arsenic, can also cause a nutritionally based seborrhoeic type of pruritus vulvae, but the condition is usually more generalized in these circumstances.

The diagnosis of a psychogenic cause must only be made, as with any other diagnosis, on positive evidence and not from the negative basis of absence of obvious material cause. Any of the skin reactions mentioned above due to physical, chemical, and microbic trauma may be present, or there may be no physical signs. These cases are related to disgust for coitus or dread of its consequences, including unwanted pregnancy and venereal disease or, extramaritally, the fear of possible family, financial, social, and moral harm that may result. In any case where a psychogenic basis is suspected it is wise to obtain the help of a psychiatrist both for confirmation of the diagnosis and for treatment.

When Professor Jeffcoate states that psychogenic causes are often merely contributory factors he raises the "egg and chicken" controversy again, because it also happens that the "egg" of psychogenic pruritus only too often hatches out the "chick's" chemical and infective dermatitis and lichenification, which cause aggravation of the pruritus and make it seem to be on superficial inspection related only to a local material cause.

A primarily psychogenic or nutritional pruritus vulvae often comes before the dermatologist in an aggravated and eczematized condition from the use of local analgesic agents (particularly benzocaine derivatives), fungicides, and germicides. These complications may be relieved by bland local treatment, but the underlying cause, if it remains, will still have to be relieved. The use of antiseptic and fungicidal applications is rarely necessary, as the infection is usually secondary. A breakdown of the skin's power of self-disinfection may result, so that in fact by their use the very condition is produced that it was hoped to prevent.

X-ray treatment has a very small part to play. It should never be used on moist, infected lesions but should be reserved for a few cases where chronic eczematization or lichenification creates a vicious circle of friction and aggravation of itching. Vulvectomy is only indicated in some cases of leucoplakia and in Bowen's disease, both of which may cause severe pruritus. In "idiopathic" cases it is as illogical as would be the excision of the tongue for tongue-biting in epilepsy. Nerve-undercutting operations and anaesthetic-injection procedures are equally irrational and are likely to lead to increasing despair when the symptom recurs.—I am, etc.,

BRIAN F. RUSSELL.

Parturition after Pneumonectomy

SIR,—Stimulated by the letter of Mr. F. Kellerman and Dr R. Sauvan Smith (October 1, p. 758) on this subject, I hasten to add another case to the one they have recorded.

A woman aged 29 had been an epileptic since 1942. Early in 1948 she developed a lung abscess on the left side for which pneumonectomy was performed on April 30, 1948. In December, 1948, she was referred to our antenatal clinic and was found to be about two months pregnant. Termination of pregnancy was advised by the chest physician, but was refused by her husband (not on religious grounds). She had previously had two normal confinements in 1946 and 1947, with male infants each weighing 7½ lb. (3.4 kg.). The antenatal period was completely normal, apart from external version being required. Labour began spontaneously on June 20, 1949, and delivery was accomplished easily after three hours in the first stage and twenty minutes in the second stage of labour. The puerperium was uneventful. On August 29, 1949, she was sterilized by vaginal hysterectomy, which is the method of choice in a multipara with a cervical or corporeal lesion such as cervicitis or subinvolution.

As pneumonectomy is a relatively new operation it is likely that there are few women who have undergone a pregnancy subsequently. However, it seems probable that their numbers will increase. While therapeutic abortion can easily be justified in these cases, yet there will be many patients who wish to proceed to term.

The antenatal period appears to be unaffected by pneumonectomy. The course of labour must be watched carefully, any delay in the second stage being terminated by forceps extraction. In multigravida with a history of previous easy labours the outcome is likely to be favourable. In a primigravida, however, with the uncertainties of the length of labour and the patient's reaction, the prognosis must be more guarded. Should there be any complicating obstetrical factor caesarean section would be almost obligatory.

My thanks are due to Mr. A. H. Siddons, who performed the pneumonectomy, and to Mr. C. M. Gwillim, who performed the vaginal hysterectomy, for their advice and assistance in this case.

—I am, etc.,

London, S.W.1. J. L. WRIGHT.

Treatment of Ringworm of the Scalp

SIR,—Dr. K. D. Crow (November 19, p. 1175) indicates that he has completely missed the point of our criticism (October 8, p. 815) of the report on the treatment of scalp ringworm with local applications, by Drs. H. Haber, R. T. Brain, and Mr. J. W. Hadgraft (September 17, p. 626). We endeavoured to draw the attention of practitioners to the fact that *x*-ray epilation is still by far the best treatment for *Microsporon audouini* scalp infections, and that the results of the treatment regime used by Dr. Brain and his colleagues were assessed on an uncontrolled series of six cases. We believed that the superiority of *x*-ray epilation was not sufficiently stressed in their recent article, though reference was made to a previous article[1] on a related experiment, and here the value of *x*-ray therapy was freely admitted. In a subsequent letter (October 29, p. 980) Drs. Brain and Haber kindly acknowledged our criticisms and endorsed the emphasis which we place on the value of *x*-ray epilation.

We do not suggest that the literature confirms our contention that 25% of cases of *M. audouini* infection of the scalp undergo spontaneous cure in less than six months. These were our own figures based on several hundred cases, but it is becoming increasingly apparent that future literature on this important point may well substantiate our claim. For example, Shaffer[2] recently stated that 70% of a random sample of 129 cases from an epidemic in Detroit which involved about 7,000 children were found to be free of infection when subsequently examined three years after the original diagnosis had been made.

We laid stress on the fact that Dr. Brain and his colleagues had only six cases of *M. audouini* scalp infection, yet they included in their trial twenty of *M. felineum* infection. We considered this to be misleading, since spontaneous cure within months is well known to occur in the great majority of cases of the latter infection.

Four cases of contact dermatitis from the total of fourteen cases assessed at the time of writing our last letter is admittedly a very high percentage. We agree that we must have been very unfortunate, but, on the other hand, we felt in duty bound to draw attention to the possibility. We can assure Dr. Crow that they were examples of sensitization dermatitis. We used 4.5% salicylanilide in a carbowax preparation kindly supplied by Imperial Chemical (Pharmaceuticals), Ltd., and essentially the same as that used by Kinnear and Rogers.[3] Dr. Brain and his colleagues mentioned local reactions presumably due to mechanical friction, but they did not mention the possibility of eczematized dermatitis.

With regard to *x*-ray epilation, Dr. Crow states that at many specialized centres there is a wait of sometimes 3–4 months before treatment can be commenced. If this is indeed the case then there exists a most unhappy situation, and it is not surprising that tinea capitis is now epidemic in many areas. On discovering our own epidemic we were quite unable to deal with all the cases which were found, but by borrowing a second *x*-ray therapy unit, and with the whole-hearted co-operation of the county medical officers concerned, we were able eventually to carry out epilations at the rate of ten cases per day. We would like here to acknowledge the help, direct and indirect, which we received from Drs. J. Kinnear and John Rogers when planning our programme.

Dr. Crow admits that the method of treatment advocated by Brain and his colleagues is suitable only when facilities exist for examination under Wood's light and, preferably, for cultures of the organism. But there must be very few such centres nowadays which do not also possess or could not borrow a superficial *x*-ray apparatus. He suggests that local treatment should be employed: (1) in all cases of pre-school age (we prefer *x*-ray epilation for all children of 3 years and over, if necessary under general anaesthesia, and we believe that cases of tinea in children under 2 years of age undergo cure with suitable local treatment in the majority of cases, and that in any event at this particular age they are seldom as likely to be a source of infection as older children); (2) when facilities for *x*-ray epilation are not available within a very short time (we agree here), and especially during epidemics (it is just in these circumstances that *x*-ray epilation is of the greatest possible value); and (3) in all cases of infection with the animal microsporon (we believe that, taking the average total duration of untreated infections as at the most about six months, all cases have to be treated on their merits; usually a quick cure in four weeks with *x*-ray treatment is preferable to a wait of some months involving laborious local therapy, as advocated by Dr. Brain and his colleagues, for in the latter event the children have to have their hair cut very short and kept short throughout treatment).

We repeat our reminder to practitioners that *x*-ray treatment is still the only reasonably certain method of cure, and we believe that great harm can be done by attempting local treatment for *M. audouini* scalp infections in any place other than an investigative centre.—We are, etc.,

J. MARTIN BEARE.
Belfast. IVAN H. MCCAW.

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2 *Arch. Derm. Syph., Chicago*, 1949, **60**, 355.
3 *British Medical Journal*, 1948, **2**, 854.

Importance of Preventive Medicine

SIR,—It is now many weeks since a leading article in your educational number (September 3, p. 524) proclaimed that "the prospects of a career in public health have never been better." And then a few lines later you wrote, "Financially the rewards . . . will always be less than clinical medicine can offer." In the interim only one or two voices have been raised to query this pronouncement, and I think that the time has therefore come to try to make the profession face the implications which it has so far accepted by remaining silent.

First I ask, Is it the considered opinion of the Association that preventive medicine is of so little importance that its remuneration shall compare unfavourably with that of therapeutic medicine? The triumphs of preventive medicine in Britain in the last century have been in their way at least equal to those of the therapeutic branch. Smallpox, typhus, cholera, enteric, and lastly diphtheria have gone or are going. The wastage of infant life has been reduced by about two-thirds. These achievements are not dramatic in the way that successful therapy may be, but they are no less real on that account. Is preventive medicine therefore of so little importance?

If the answer to my first query is in the affirmative, the second must be squarely faced. Does the medical profession claim a vested interest in sickness? The only justifiable ground for casting aside preventive medicine is that it is ineffective. If it is conceded to be effective then it must be given adequate encouragement of all kinds. If they consider it to be effective but not worth equal financial encouragement it is then a legitimate criticism of the therapeutic branch that they want the public to be ill in order that the doctor's livelihood shall not suffer. If, on the other hand, the profession as a whole agrees with preventive medicine in theory and practice, what are they doing to see that the necessary encouragement is given?

It took a year to wring agreement to negotiate from the local authority associations, and after four further months the machinery for negotiation is not ready. Our colleagues in the Civil Service have the necessary machinery, but apparently it cannot be made to work, and they are as badly off. This is not good enough, and calls for an awakening of the medical conscience of every Division and Branch of the Association as

well as in B.M.A. House. If prompt and effective action is not forthcoming the medical services of the central and local authorities will go where the school dental service has already gone—down the drain. The economic pressure is just as great on the doctor as on the dentist, but the opportunity to transfer from prevention to cure less easy to find.

If the local-authority medical services go the way of their dental counterparts there will be the immediate risk of the return of diphtheria on a substantial scale and also of the reappearance of the other epidemic diseases. As a parting shot I want to ask if any of my general-practitioner friends want to have to cope with an outbreak of smallpox without the help of their local health department.—I am, etc.,

Elgin, Moray. I. C. MONRO.

SIR,—How very refreshing to read of Professor R. H. Parry's frankness on proposing the toast of the guests at the Society of Medical Officers of Health Annual Dinner (*Journal*, December 3, p. 1289). Most of us in the public health service are getting just a little tired of the soft soap and treacle regularly handed out to us by every non-medical functionary in the land from the Minister downwards. Everyone loves us, everyone says we are doing a grand job, everyone is awfully sorry for us—and no one does a thing about our status except, of course, talk about it endlessly.

Week after week we read of practitioners struggling for increased remuneration. Good luck to them. But is it really realized that any practitioner the day after he qualifies is a better financial prospect than the medical officer of health who has a specialist diploma and years of experience behind him before he gets his post as M.O.H. with its attendant pittance?

Why have not the associations of local authorities the boldness to come out into the open and say what is pretty obvious anyway—that they don't want a public health service? Then we could all clear out and let it collapse as ignominiously as the school dental service has done, and the rest of the profession could busy itself in trying to patch up ills which would never occur if preventive medicine offered even reasonable inducements and a living wage for anyone but visionaries and lunatics.

Is it not a little ironical that the very body of medical men who started a public health service in this country should be the only ones to be disregarded when the National Health Service Act came into being? Let us have the answer one way or the other, and soon. We don't ask very much—only to be equated financially with other medical men of comparable experience.—I am, etc.,

Wallingford, Berkshire. HECTOR MACKENZIE-WINTLE.

Dangers of Dicoumarol

SIR,—The new coumarin substance, B.O.E.A., described by Drs. Catherine C. Burt, Helen Payling Wright, and Mirko Kubik (December 3, p. 1250), is clearly a more quickly acting and in some ways a safer anticoagulant than dicoumarol. In view of this article and of the leading article entitled "Dangers of Dicoumarol" (p. 1279), I think three important questions need answer. What is the most effective and safest prothrombin level to aim at? How often is it necessary to estimate the prothrombin level? How dangerous are these anticoagulants?

In the article by Dr. Burt and her colleagues a prothrombin level between 20 and 30% was aimed at because it was thought "generally desirable," but in some cases a level of 40 to 50% of normal "proved satisfactory for clinical improvement." A number of workers[1–4] have all aimed at a prothrombin level of 10 to 20% of normal in the treatment of thromboses. Peters and his colleagues[5] produced a level of 35 to 50% in their cases and recorded good results. Scott and Lissimore[6] described a case of lymphatic leukaemia with multiple mesenteric thromboses which ceased when the prothrombin level was kept between 60 and 70% of normal by dicoumarol. Treatment was maintained for over three years, prothrombin estimations being made at monthly intervals.

During the last four years I have treated 81 cases of thrombosis by maintaining a prothrombin level of 65 to 75% of normal, and the results have been as good as any of those recorded by the authors quoted above for similar cases. No haemorrhage has been observed. These authors have all recommended daily estimations of prothrombin level, and as their patients were constantly in close proximity to haemorrhage this was certainly essential. On the other hand, when one aims at a level of 65 to 75% of normal, dosage can be adjusted to produce this level and maintain it, using the prothrombin estimation to confirm one's aim rather than as an essential in treatment. Estimations in these cases were never done more often than every five days; in prolonged treatment estimations were done once a month. The prothrombin level never fell below 50% and never rose above 80%. In 24 cases treatment has been continued for at least six months of the year for one to four years.

These cases have all been treated at home, but no case in which liver or renal damage has been found or suspected was given dicoumarol without more frequent prothrombin estimations. Shapiro and his colleagues[7] showed how liver damage increased the response to dicoumarol. Richards and Steggerda[8] demonstrated the continued effect of dicoumarol in rats from which the kidneys had been removed; normally the prothrombin level soon falls.

Dr. Catherine Burt and her co-workers also report that no gross cumulative effect of B.O.E.A. has been observed. Bingham and his colleagues[9] found the same with regard to dicoumarol. After taking 10 g. of dicoumarol in 92 days, a man with thromboangiitis obliterans had normal liver and renal function. My patients who took dicoumarol for six months during each of four successive years similarly showed no ill effect, their white and red cells remaining normal.

It is suggested, therefore, that a prothrombin level of 60 to 75% of normal is adequate for the treatment of most cases of thrombosis; that prothrombin estimations in these circumstances are unnecessary more often than every five days in most cases; that dicoumarol and also B.O.E.A. given for a prolonged time are not harmful in correct dosage.—I am, etc.,

Leeds. R. A. MURRAY SCOTT.

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Enteritis Due to Duck Eggs

SIR,—The article by Professor L. P. Garrod and Dr. M. B McIlroy on enteritis due to duck eggs (December 3, p. 1259) raises certain problems of prevention. Is there any conclusive evidence that a duck infected with *Salm. typhi-murium* ever transmits infection to the inside of a freshly laid and undamaged egg?

In the article in question the words, "In hens' eggs contamination is confined to the outer surface of the shell," suggest that this may also be the path of infection in duck eggs, facilitated in the case of duck eggs by the greater porosity of the shell and by the conditions under which a duck may lay its egg. Unlike a hen, a duck as often as not does not lay its egg in a nest but anywhere about the farm. In addition, a duck's droppings are almost invariably liquid, and this liquid faecal matter gets trampled over the egg.

Even under these conditions it is highly improbable that the egg will become infected unless it is left lying out for a matter of days, and it is on dirty farms that this is likely to occur. It is these "found" eggs which may have been lying out for an indefinite period which are probably the cause of human infection.

An egg, be it duck or hen, which has been lying in one position for some days tends to become sided-yolked, and when, as happens to all eggs at packing stations, these eggs are lamped and found to be sided-yolked they should be discarded, although this would entail discarding some fresh eggs.

It should also be borne in mind that most cracked, broken and stained eggs are, at packing stations, turned into what are known as "liquid eggs" and sent to bakeries and caterers.

hence the greater liability to infection even from a "queen of puddings." Lastly, distribution being as it is, it is unlikely that the two hundred eggs delivered to St. Bartholomew's were less than a month old.—I am, etc.,

Hittisleigh, Devon. F. E. GRAHAM-BONNALIE.

Chilblains

SIR,—I read Dr. J. T. Ingram's contribution, concerning chilblains, to the "Refresher Course" (December 3, p. 1284) with increasing interest, for it occurred to me while reading this article that chilblains may eventually be classified as one of the minor and localized diseases of adaptation.[1]

As Dr. Ingram states, "Exposure to cold and damp followed by warmth" is the common precipitating factor for chilblains. Exposure to cold is one of the "alarming stimuli" described by Selye. The psychological and nervous influences mentioned by Dr. Ingram could act via the pituitary and the "endocrinotropic" hormones in the same manner that Selye postulates nervous fatigue acts in the alarm reaction.

Finally, the susceptibility for the development of chilblains at puberty, the menopause, and old age and their virtual non-appearance during pregnancy are very suggestive of an endocrine mechanism. It was indeed the remissions of rheumatoid arthritis during pregnancy and jaundice that led Hench to his brilliant observations concerning cortisone.

It would be interesting to know the incidence of chilblains in rheumatoid subjects as compared with that in normal people, and also whether anyone has yet observed a dramatic resolution of a chilblain in a patient treated with cortisone.—I am, etc.,

London, W.5. M. D. WARREN.

REFERENCE

1 Selye, H., *Practitioner*, 1949, **163**, 393.

Resettlement of the Tuberculous

SIR,—The views of Professor Frederick Heaf on rehabilitation of the tuberculous need no bolstering from me against the oblique attack of Dr. Alice Stewart (December 3, p. 1294). It is, however, disheartening to learn that, emanating from "the city of lost causes," philosophic doubt is being cast on the worth of all our policies and schemes in regard to rehabilitation. Misguided these may be, but their fulfilment is at least practicable and realistic. If, as an alternative to the wise and timely reinstatement of tuberculous persons in industry or office, Dr. Stewart can only offer the suggestion of keeping them permanently "in affluence," then she should withdraw from the industrial Midlands and North along with her impedimenta of mass radiography and morbidity tables.

Will she define "affluence" not in the *O.E.D.* sense but in terms of the needs of a tuberculous wage-earner and his wife and family? The standard rates of pensions, sick-pay, and national assistance provide little more than subsistence. Increases have been granted by (or wrung out of) successive Governments sporadically and lagging in time behind the rise in the cost-of-living index. Does Dr. Stewart really think that in future tuberculous persons will be assisted by the State with more than the wherewithal of bare existence? Pensioning-off, however generously, our tuberculous population will not abate by one jot their infectivity in society and in their homes, clubs, churches, and cinemas. Man works for 44 hours, sleeps through 60 hours, and is at home or mixing gregariously with his fellows for 64 hours each week. There is no evidence that exclusion of the tuberculous (even if it were possible) from all work activity would diminish the total infectivity existing in the community. On the contrary, granted eight hours more leisure daily they might well have more opportunities of sowing infection outside workshop or factory.

Half of the tuberculous population becomes capable and does resume work eventually; the work may require to be modified or altered. One-sixth are dying cases, are aged, or are dependent married women. Only the remainder, consisting of 20,000 to 30,000 chronic active cases of pulmonary tuberculosis, need consideration in our rehabilitation plans. Many of them have good work capacity and tolerance. Most are entering or are already at the stage of full productive life. It would be inhumane to deprive these people of opportunity to work and to treat them as "superannuated" men and women at or before the prime of life.

No one, least of all Professor Heaf, advocates the indiscriminate replacement of the tuberculous in industry. Our young people going straight from school to work-bench, shop, or office there to work alongside older persons, must be protected at all costs. Dr. Stewart's finding of 7 "open" cases in a boot and shoe factory is not germane to the issue unless she also indicates the size of the population that was surveyed or at risk. She decries our present "industrial schemes." To which does she refer? I would draw her attention to the plans of the Disabled Persons Corporation, which has already set up special "Remploy" factories for the tuberculous and aims at establishing one or more in each region. Hull's factory was the first to be opened in the country. It has operated for nine months, has places for 250 men and women, and 60 men are now working there. I can testify to the increased well-being and morale of men who are now being afforded for the first time the chance to work within their reduced physical capacity. As a reward they take home a wage packet on Fridays, earned by their work and skill, instead of being the passive receptors of their "allowances" at the Post Office on Mondays.

Some of the desiderata enumerated by Dr. Stewart in the earlier part of her letter are surely not impossible to attain. I refer to more adequate housing and improved standard of life for tuberculous and healthy alike. These and other social betterments are the prerogative of none, but are within the rights of all to obtain or possess. I assume that Dr. Stewart's letter was intended to be provocative. If her suggestion that it might be better to superannuate tuberculous men and women as a means of reducing the reservoir of tuberculous infection in this country is seriously advanced, then I trust that this latest "Oxford movement" will die a premature and unhallowed death.—I am, etc.,

Hull. ROBERT HARDY.

Rh Genotype Tests

SIR,—Dr. Edgar Rentoul (December 3, p. 1300) refers to the production of evidence with regard to the Rh sub-groups as being used in a British court for the first time in a medico-legal case recently heard in a Scottish Sheriff Court. Although Dr. Rentoul does not state the date of the hearing, which has otherwise escaped my attention, I gather it was more recently than June 8, 1949, when I gave such evidence at a magistrate's court. The facts of the case were as follows.

A woman who had previously borne an illegitimate child alleged that as a result of a single act of intercourse following a casual meeting she had become pregnant. The defendant, who admitted the act, alleged that a contraceptive sheath had been used. The probable time of conception corresponded with the admitted intercourse.

It has been my practice to test for all the antigens for which I have been able to obtain antisera in disputed paternity cases which I have investigated, but this was the first occasion on which an Rh sub-group had produced evidence of value. The results of testing in this instance were as follows:

	A	B	C	D	E	c	M	N	S
Baby ..	+	−	++	++	++	++	+	+	−
Mother	+	−	++	++	−	?−	+	+	+
Alleged father	+	−	++	++	−	(+)	−	+	−

The result obtained on the mother's corpuscles with the anti-c serum available was a doubtful negative reading, and a very active anti-c serum was not available at the time. Because of the uncertainty of this result an attempt was not made to genotype the individuals, and the evidence was considered to be unsuitable for medico-legal work. The evidence was accepted by the magistrates and the claim dismissed as not proven.—I am, etc.,

Newcastle-upon-Tyne. T. H. BOON.

POINTS FROM LETTERS

Spoons as a Measure

Dr. E. H. JEANES (Rotherham) writes: I was pleased to see the letter of Dr. J. M. Hamill (November 19, p. 1180) regarding the very important matter of spoon measurements. The misconception about the size of the tablespoon is a very common one and can in certain circumstances lead to most unsatisfactory treatment. The position is confused because textbooks often reiterate the myth that one tablespoon contains half an ounce of fluid, whereas in fact it contains one ounce. Contusion is doubly confounded because the majority of medicine bottles are now not marked in tablespoon doses, and the patient has to measure his own dose. . . . Where bottles have been graduated in tablespoons the proper dose is taken, because the patient relies on these bottle markings, yet let it be noted that these measurements are in fact dessertspoon doses, as can be verified by anyone with the interest to do so. It would not be difficult to find prescriptions in the *National Formulary* which would cause definite harm if twice the prescribed dose were taken regularly. The instructions on tins containing dried milk may be misleading. For instance, an infant weighing 8 lb. is started on artificial feeding and the mother is instructed by a nurse to feed by the directions given on the tin. Since some of the leading dried-milk manufacturers give directions in tablespoons of water to be added, the mother proceeds to make the feed by adding four measures of dried milk to eight tablespoons of water. This is poured from a jug into a feeding bottle and given to the baby. The baby, naturally, can only take half the amount, and the result is underfeeding, since only two measures of dried milk are taken. Of course feeding bottles are marked nowadays, but there still exist certain mothers who rely solely upon their own tablespoons and not on the markings on the feeding bottles. It is unfortunate that the Ministry of Food in its instructions issued with National dried milk has repeated the common fallacy that "two tablespoonfuls of water equal about one ounce." It is, of course, two dessertspoonfuls which equal one ounce.

Death by Hanging

Dr. R. PAKENHAM-WALSH (Lancaster) writes: I was interested to read Dr. F. A. Richards's letter (November 26, p. 1235) suggesting that death by hanging was not as instantaneous as is generally supposed. The same thought occurs to me every time I have the unpleasant duty of executing one of my hens by the process of breaking the neck as near to the occiput as possible. Even when everything goes according to plan the hen gives every appearance of being conscious for a few seconds after the neck has been broken. Its eyes remain open and then gradually close, as though the creature was dying slowly. The subsequent "P.M." always shows a considerable haemorrhage in the region of the break, and it is probably this which causes the head and its owner to become finally dead. On one occasion I was anxious that a special pet hen should not suffer, and I was horrified to find that I had pulled the head right off. Death, however, had been instantaneous, as the head was certainly dead by all appearances, while its owner still remained very much alive.

Fracture of the Olecranon

Dr. L. S. WOOLF (London, N.W.11) writes: Thirty years ago the patient of whom I write, then a man of about 30, fell off a bicycle on to his left elbow. An *x*-ray examination showed that the fractured olecranon was drawn up about 2½ in. (6.25 cm.) from the body of the ulna—i.e., there was a separation of 2½ in. between the olecranon and the body of the ulna. It was decided that mechanical means of bringing the fragment of the olecranon down to join the shaft of the ulna would suffice, and an open operation would thereby be avoided. Straps were applied to the upper arm exerting tension on the triceps, and after a short time it was considered that the olecranon was near enough to the shaft of the ulna to form a fibrous union. This in fact is what took place, and the patient had no functional disturbance in the use of the limb. From time to time there was "rheumatism," but it was only recently that there was much pain in or around the elbow. Because of this an *x*-ray photograph was taken, and this revealed that there is, after thirty years, still no bony union, although function is practically perfect.

Pruritus Vulvae

Dr. H. THISTLETHWAITE (Sedbergh, Yorkshire) writes: In Professor T. N. A. Jeffcoate's learned article on pruritus vulvae (November 26, p. 1196) I find no reference to the application of testosterone ointment. A number of my women patients, whose ages range from 30 to 90 years, have cause to bless this ointment, which was recommended to me in the first case by a gynaecologist and has fully justified itself after other measures have failed lamentably. A single treatment which has given relief to some victims of pruritus vulvae deserves to be more widely known and used.

Obituary

WILLIAM ANDERSON, O.B.E., F.R.C.S.

Mr. William Anderson, senior surgeon to Aberdeen Royal Infirmary, died suddenly on November 29. He was born in Aberdeenshire 63 years ago, of a farming family. In 1904 he entered Aberdeen University, and graduated in 1909 with distinction in his final examinations; he was awarded the gold medals in both medicine and surgery. After graduation he held hospital appointments in the Royal Infirmary and the Sick Children's Hospital. He became house-surgeon to the late Sir Henry M. W. Gray, to whose influence and inspiration, like so many of his generation, he owed so much—a debt which he always gladly and thankfully acknowledged. Then followed a period of postgraduate study in Germany in the surgical clinics at Tübingen and Berlin.

In 1913 Anderson was appointed to the honorary staff of the Royal Infirmary as anaesthetist—in those days a recognized stepping-stone. In the first world war he served for some four years in France, at first as a regimental medical officer and later as surgical specialist in charge of the surgical division of No. 12 Stationary Hospital. During the war he acquired a comprehensive experience as a general surgeon, though even at that time his main interests were tending to focus themselves on abdominal and thoracic surgery, and by the end of the war he had established his reputation as one of the most promising younger surgeons of the day. For his services he was mentioned in dispatches and awarded the Order of the British Empire. In 1919 he returned to Aberdeen and was appointed assistant surgeon to the Infirmary, again in the service of Sir Henry Gray, and he also joined the surgical staff of the municipal hospitals. In 1912 he became a Fellow of the Royal College of Surgeons of Edinburgh, and in 1923 of the Royal College of Surgeons of England. In 1928 he was appointed examiner in surgical pathology and operative surgery for the diploma of F.R.C.S.Ed. He rapidly acquired an extensive surgical practice and a steadily increasing reputation as a clinical teacher.

At the outbreak of the second world war he became surgical director to the Northern and North-Eastern Areas, but it was obvious to his friends that he would not be content for long with a purely civil appointment, for his heart was set on service in the field once again. Early in the war he was appointed consulting surgeon to Scottish and Northern Ireland Commands with the rank of brigadier, an appointment for which he was peculiarly well fitted by his experience in the first world war, his shrewd common sense, and his ability to sum up men and affairs. Even on a physique as robust as his the heavy responsibilities and the constant journeying to Ireland and all parts of Scotland must have taken a heavier toll than at first appeared.

At different times Anderson held many other important appointments—he was president of the Association of Surgeons of Great Britain and Ireland from 1941–4; an original member and later president of the Society of Thoracic Surgeons of Great Britain; and inspector of examinations for the General Medical Council. He is survived by his widow, two daughters, and one son, to whom all will extend their sympathy.

A.G.A. writes: By the sudden death of William Anderson Aberdeen medical school has been deprived of the services of

a great surgeon and a great clinical teacher; his colleagues and students, both past and present, have lost a great and loyal friend. He had spent the whole of his professional life in the service of Aberdeen Royal Infirmary, with the exception of some eight years of distinguished military service in the two world wars. I had the privilege of enjoying his friendship and of being closely associated with him since he entered the university as a first-year student in 1904.

In his later years he would often refer to the first world war as one of the most formative periods of his life, and he was proud of having begun his military career as a regimental medical officer. No doubt it was the fruits of that training combined with his native shrewd common sense and his wide clinical experience which made his opinion as a consultant in the second world war of so much value to his patients, his colleagues, and his country.

On his return to Aberdeen in 1919 he threw himself with his accustomed zest and vigour into the work of the hospital—teaching, operating, spending long and arduous days in the out-patient department, performing research at the Rowett Institute, playing hard and working hard. He had an enormous capacity for hard and sustained work, and he could spend hour after hour in the operating theatre without the least sign of fatigue.

The immediate post-war years to him were one of the happiest periods of his life. As a teacher he rapidly made a name for himself, and in his teaching he was outstanding—clear, concise, and practical. If in his later life one ventured to suggest to him the advisability of taking things a little bit easier, particularly in giving up his emergency operating and his evening clinics on his receiving days, he would invariably reply that he believed this was one of the most important parts of his teaching, and in this I am sure he had the assent of all who were privileged to attend them. With his students he was approachable; he was friendly and profoundly interested in all that concerned them in their work and play. He was equally happy in presiding at the students' medical society, to which he supplied a constant stream of inspiration, or presiding at the boxing matches, which he thoroughly enjoyed.

Nowhere was his broad and generous humanity seen to better advantage than in his superb handling of patients. With his pawky good humour, his facility in the use of the Doric, he could rapidly put the most nervous patient completely at his ease, and completely win his confidence and gratitude. He remained a general surgeon to the end of his days, although it was perhaps in abdominal surgery that his masterly technique, his resourcefulness, and his courage were seen at their best. He travelled in Europe and America, always eager to keep abreast of the latest developments. At one time he paid particular attention to the developing specialty of neurosurgery and laid the foundations of a neurosurgical unit in Aberdeen. Later he was to return to one of his earlier interests, the development of thoracic surgery, and he must have been one of the first surgeons in Scotland to undertake thoracoplasties, of which he did a great many for the Red Cross sanatoria.

His contributions to literature were comparatively few, for in his busy and active life there was little leisure, and temperamentally he was more interested in the art of surgery and in the individual patient.

Mr. A. Graham Bryce writes: One of those who made a special study of chest surgery while they continued their practice in the general field, Anderson applied himself to his specialty with all the devotion of his honest being. He was an original member of the Society of Thoracic Surgeons of Great Britain and Ireland, and the fortunes of war kept him a member of its executive committee till a few weeks before his death. It was a stubborn obstacle indeed which prevented Anderson from making the long journey from Aberdeen to attend a meeting of the society or of its committee. The opposite of a thruster, he only took part in debate when he really had something to say. It was in the more intimate and informal group round a table in a hotel lounge that his wisdom and wide experience found expression. In committee his constant thought was for the younger men, for whom he was ever ready to efface himself. Of all the qualities which endeared him to his fellows, and for which he will be remembered, his humanity was the most outstanding. There will be a sense of something wanting in any assembly of thoracic surgeons which lacks the cheer of Willie Anderson's presence.

A. M. writes: By the sudden death of William Anderson the medical school of Aberdeen has lost one of its most prominent and useful members, a loss which will be shared by his many friends and patients. His professional achievements are well known, but, as one who was associated with him since his student days, I would like to pay tribute to some of his personal qualities. He set for himself a very high standard of professional work, and gave freely of his time and energy in the care of his hospital patients and in teaching his students. To his colleagues he was always ready to give help when it was needed. Integrity of thought governed his actions, and he was quick and candid in his resentment of anything which he considered unfair or unjust. He had a most generous nature which many of us had occasion to appreciate, and we feel that our world will be the poorer by his loss.

Sir Leonard Rogers writes: The notice of the late Professor C. A. Bentley (December 3, p. 1299) deals fully with his earlier work on malaria and kala-azar. May I add a few lines on his later, and more important, work while Director of Public Health in Bengal on the control of cholera by inoculation. In December, 1923, he issued a circular on anti-cholera inoculation in the Near and Far East, which illustrated its value, and in May, 1927, one entitled "Cholera must be stamped out of Bengal." After five years' struggle—with the support of a new Governor of Bengal, Sir Stanley Jackson, who had made himself acquainted with recent epidemiological work on cholera in India—Bentley obtained sanction for a laboratory to make cholera vaccine at one-eighth the price of that previously supplied, and in 1928 he organized the inoculation of over 2,000,000 people in Bengal—far more than in the whole of the rest of India. Many instances of the rapid suppression of cholera outbreaks in Bengal villages following inoculation first popularized the method in India. It included instances of controls shown by the immediate decline of the disease in inoculated Hindus, but its continuance among Mohammedans in the same village, who had refused inoculation. It was largely due to the enthusiastic work of Bentley that the long neglect in India of anti-cholera inoculation was gradually overcome—work in which his administrative ability was outstanding and work which will form a permanent memorial to him.

When visiting Greece in August this year Dr. Ludwig Guttmann, clinical director of the Spinal Injuries Centre, Ministry of Pensions Hospital, Stoke Mandeville, delivered a lecture on paraplegia to Army medical officers at Athens at the request of the Greek Minister of War and the Director-General of the Greek Army Medical Services. Dr. Guttmann has now been invited by the medical authorities of the Government of Israel to advise on the organization of a centre for the treatment and rehabilitation of paraplegics. He is spending about three weeks there.

Medical Notes in Parliament

NATIONAL HEALTH SERVICE (AMENDMENT) BILL

The House of Commons considered, on December 9, amendments to the National Health Service (Amendment) Bill accepted by the House of Lords on November 17 (*Journal*, November 26, p. 1239). The Bill was read a third time in the House of Lords on December 2 (December 10, p. 1359).

Mr. BLENKINSOP said the new Clause "A" was inserted to enable the Minister to make regulations adding to the functions of the Medical Practices Committee. Its functions in relation to the distribution of doctors were limited by statute to granting applications by doctors not already on the medical list for inclusion in that list. Where several doctors applied to fill a vacancy it might be held that the Medical Practices Committee was only concerned strictly with applications from outside the area, whereas it had been usual for the Medical Practices Committee to consider applications from wherever they might come and to make its decision on the qualities of the applicants. Experience had shown that an extension of functions might be desirable in one or two other cases. In England and Wales the view was taken that a doctor whose application to employ an assistant was refused by the executive council should have the right of appeal. It seemed to the Ministry that the Medical Practices Committee should have power to determine such appeals. These matters had received the full consideration of the medical profession. Any other similar evidence of the powers and functions of the Medical Practices Committee would also receive the consideration of the medical profession before any changes in regulations were proposed.

Sir HUGH LUCAS-TOOTH said that there should be some statement from the Government that it was not intended to use the wide wording of the amendment to take additional powers for the Medical Practices Committee without giving Parliament an opportunity of considering what those powers should be.

Mr. BEVAN intervened to say there would be regulations which would be laid before Parliament, and the House then agreed to the new Clause.

Charges for Prescriptions

A second new Clause "B" was then debated. It dealt with the recovery of charges in respect of pharmaceutical services:

"Regulations may provide for the making and recovery, in such manner as may be prescribed, of such charges, in respect of such pharmaceutical services, as may be prescribed, and may provide for the remission or repayment of the charges in the case of such persons as may be prescribed."

Mr. BLENKINSOP said the amendment was designed to give statutory authority for the Prime Minister's proposal to make a charge for prescriptions under the National Health Service. The Clause was drafted widely because the exact nature of the arrangements had not been decided. Discussions were proceeding. It had been announced that the charge would not exceed one shilling, and that old-age pensioners would be relieved of the charge, as would ex-Service men who were war pensioners. They would continue to receive free treatment for their war disabilities. The Government had under consideration many representations made by members of the House and others on the detailed working of the scheme.

In the House of Lords it had been suggested that there had been overprescribing by doctors. On that point he could say that there was already a joint committee of the Central and Scottish Health Services Committee to advise Mr. Bevan whether it was desirable and practicable to restrict in any way the prescribing by doctors of medicines of doubtful value and of unnecessarily expensive brands of standard drugs. The Ministry could not make any statement on this till recommendations had been made.

Mr. WALTER ELLIOT said the Opposition did not oppose the amendment, but it should not pass without comment. It would place 19,000,000 people in a worse position than they had been in since July, 1948, and a considerable number of people in a worse position than since 1912, when insured persons were allowed to obtain their prescriptions without this charge. He understood that £10,000,000 would be obtained by this charge. Was that figure still intended? When might the House expect the regulations to be laid? Would they be laid during the prorogation of Parliament?

These regulations would have the force of law as soon as they were laid, and Parliament would require the earliest opportunity to debate them thereafter. He asked whether the sums to be raised by this procedure would obviate the need for a supplementary estimate for the Ministry of Health. Was there any intention to extend the category of hard cases beyond old-age pensioners and ex-Service men who were war pensioners?

Mr. Bevan must, he thought, have determined whether the charge was to be based on each prescription or on each prescription form. The average number of prescriptions was three on two forms. It was desirable to know whether the prescription form or the prescription was to be charged. Was the shilling to be charged on a flat rate or a graded rate? A great number of prescriptions were inexpensive, and on those inexpensive prescriptions the pricing machinery was now in difficulties. He was delighted to think that Mr. Bevan did not accept an increase in prescriptions as an improvement in the health of the country. If small prescriptions were to be priced on a graded figure the difficulty with the chemists would be increased. The Minister should be able by this time to give a lead on these matters.

Mr. FRANK BYERS said he had come to the conclusion that the Lords amendment should be rejected. The House should beware of giving to any Minister powers which could not be examined in detail. What about the difficulties when rural practitioners dispensed their own medicines? What about diabetics who required continuous treatment? He wanted proposals to be laid before the House in a form in which they could be amended in detail. He did not think the scheme would work. If the charge was too high it would cause injustice, and if it was too low it would not remove the abuses.

A Retrograde Step

Dr. SANTO JEGER said he was one of the few medical men in the House who still followed his profession regularly. He regarded the charging for prescriptions as a completely retrograde step. They had encouraged everyone to become health conscious and had said that if people had small ailments they should seek consultation early, but the charge on prescriptions was introduced as a deterrent.

He feared that Parliament would deter the wrong persons from going to the doctor for treatment. A doctor might have to prescribe five or six items for one ailment at one time—for example, for boils. Was a man with a boil to be asked to pay five or six shillings for treatment? Mr. Bevan had talked of cascades of medicines being poured down people's throats. They all knew that a medicine was often given purely as "a mental poultice." It was not always possible for a doctor to eliminate a patient's fears by words. Part of what the doctor had to do was to supply a prescription, a placebo.

Were old-age pensioners who continued in work to be exempted or were they to pay for their prescriptions? Who was to ascertain whether patients were to be exempted? He did not think the doctor would agree to do it, and the chemist should not be required to ask people to produce their birth certificates or to show whether they were drawing the old-age pension. The Minister had received representations from both the British Medical Association and the Socialist Medical Association. He did not think that these two bodies had ever been in agreement before, but they were definitely in agreement on this.

He could show the Minister many ways in which both doctors and patients could avoid this charge. Another, more serious aspect was that any attempt to limit general practitioners to drugs on a standardized list and to prevent them from trying out unestablished drugs would suppress original work.

Mr. BEVAN asked whether Dr. Jeger asserted that, if a committee of responsible members of the medical profession said an ingredient sold under an expensive title was exactly the same as an ingredient sold under a less expensive title, the Ministry

should adopt the idiosyncrasy of a general practitioner and pay the inflated price.

Dr. JEGER agreed that when there were two preparations one should, other things being equal, use the cheaper one.

Mr. BEVAN hoped Dr. Jeger would not pursue the matter further or he might prejudice discussions which were going on. If Dr. Jeger said that in no circumstances could there be an official list of drugs provided by a responsible, authoritative order, he went further than his friends would wish him to go. The amendment under discussion had nothing to do with such a list. It referred to the power to enforce a charge.

Dr. JEGER said that he was prepared to accept what Mr. Bevan had said and not pursue the matter. He declared that in his experience there had been little abuse of the Service. When all possible exceptions had been considered little of the expected £10,000,000 would await collection. If the proposal went through, patent-medicine vendors would find their sales going up by leaps and bounds.

Mr. LINSTEAD, as secretary of the Pharmaceutical Society, thought that the Minister should explore the possibility of "pay as you use" rather than make cuts in the hospital service or hold up the rebuilding of hospitals. But the House should not be asked to go too far in approval of the scheme without knowing in more detail how Mr. Bevan proposed to carry it out. He hoped that the Minister proposed at an early date to bring chemists into the discussions. At present they did not know where they stood. Estimates for the pharmaceutical services were originally £6,000,000 but were now £20,000,000. On those figures the Minister was entitled to see whether something could be saved to the Exchequer. He asked whether a prescription made out for a mother and two children ranked as one or as three. Hundreds of thousands of such prescriptions were written in cases of family sickness. Group prescriptions could be written if there was an epidemic in a school. A doctor might write one for 60 patients. Did that rank for a charge of 1s. or 60s.? His view was that there must be a flat-rate charge, not one graduated according to the value of the medicine. It would be impossible for pricing officers to attempt to make an assessment according to the value of the medicine. The most they could do was to count the forms.

If patients who went to a general practitioner were to be charged, what of the out-patients at hospitals? The last thing they wanted to do was to divert patients from the general practitioner to the out-patient departments of hospitals. There was the problem of the rural doctor. Diabetics had been mentioned, but what about epileptics, people with chronic bronchitis, and the chronic sick generally?

If there was to be a straightforward payment of 1s. when the medicine was handed over the counter the system might possibly work. But if the "pay as you use" principle was justified for the pharmaceutical services it was justified for the dental and ophthalmic and other benefits.

Each According to his Shilling

Mr. SOMERVILLE HASTINGS asked whether the House was going to replace the Socialist principle of "Each according to his need" by "Each according to his shilling." He had found that a little more than half the doctors with whom he had discussed the question had agreed that there had been some abuse. But doctors who said there had been considerable abuse were those who had opposed the scheme from the start. He asked Mr. Bevan whether neurotic people would be deterred by a shilling and robbed of the enjoyment of bad health. One of the people who would be deterred was the poor mother with young children. Doctors were very concerned about the interests of their patients, and in order to save the shilling poor patients might be given enough medicine for a month rather than for a fortnight. More medicine would be ordered rather than less.

The great advantage of a free and universal service was that doctors got hold of illness earlier, and in medicine that a stitch in time saved nine was a truth more important than ever now that so many bactericidal drugs had been introduced. He agreed with Mr. Bevan that some doctors were inclined to order proprietary medicines when an identical cheaper medicine would do as well. The public did not understand how busy the drug houses were in sending their travellers round to doctors. If the Minister gave the doctors lists of equivalent drugs and asked them to supply these to their patients he would save the necessary money and the good name of the scheme.

Mr. SOLLEY contended that the excuse for the order from the Treasury to Mr. Bevan to save £10,000,000—unnecessary resort to doctors and chemists—could not stand investigation. The Minister of Health should have asked himself before putting this burden on the working class whether he could not save the money by taking away some of the profits of the chemical and pharmaceutical manufacturers. The charge must cause great hardship to chronic patients. He would vote against the proposal and would fight on that issue at the General Election.

Administrative Difficulties

Mr. BEVAN sympathized with those Members who had said they did not know how the power which was requested would be used., He himself did not yet know all the answers. The proposal to make a charge up to 1s. created no administrative difficulties. These arose out of the exemptions. It was no economy to transfer a charge from the State to the individual. The proper economy was to introduce a more efficient way of giving the service.

The Government wished to take power to make a charge for the pharmaceutical service alone because this was the part of the scheme where the greatest load had fallen and in which the scheme was inclined not to give the standard of service which the Government required from it. The amendment did not give power to impose a charge. It was to restrict the free service on the pharmaceutical side up to 1s. The National Health Service would pay the cost of a prescription above a shilling. Even with this charge the National Health contributor would have a far wider range of service than was ever available before.

The Government had come to the conclusion that it would be glad to reduce the queues at surgeries and the unnecessary expenditure at chemists' shops. Some of the abuse arose on aspirins, bandages and so forth, costing less than 1s. The proposal had not been received with much indignation because there was awareness of the abuse which had been taking place. The Government must presume that it was not in the interests of the patient to have too many prescriptions. He was not suggesting that the new clause ought to be a permanent feature of the National Health Service. It was put forward as a temporary easement with a residual financial advantage. The figure of £10,000,000 assumed no exemptions, and any exemptions would reduce that amount. The House would have an opportunity of discussing the regulations before they were put into effect. There was evidence already of a reduction in some cases of the burden on the general practitioners.

Mr. HASTINGS asked whether, in view of that reduction in the abuse that he had mentioned, Mr. Bevan would consider that it might be unnecessary for him to introduce these regulations.

Mr. BEVAN replied that he was giving consideration to this. He was not anxious to burden himself with a complicated administrative machine if he could achieve the same results by other means.

Dr. SEGAL contended that, if the suggested charge steadily reduced the number of prescriptions, in a few months it might save more than £10,000,000. If the present total of 187,000,000 prescriptions a year could, at the end of twelve months, be reduced by 30%, the need for the imposition of a charge would have vanished.

Mr. PIRATIN contended that no one could give evidence that abuse existed in prescribing.

Mr. SPARKES referred Mr. Piratin to the report of the Estimates Committee on the administration of the National Health Service.

Mr. PIRATIN said he was not surprised to see a united front between the B.M.A. and the Socialist Medical Association. He drew attention to the profits made on medicaments. He said that Glaxo Laboratories, which produced penicillin, made, in 1948, a gross profit of £1,641,000 and a net profit of £660,000. In 1949 the gross profit was £2,605,000 and the net profit £930,000.

There was the case of "dexedrine." It was first introduced by Menley and James at 126s. per 1,000. The tablets were shortly afterwards marketed by Ward Blenkinsop at 31s. per 1,000. In the last few weeks Boots marketed the same preparation at 8s. 6d. per 1,000. Procaine-penicillin was first sold in this country by I.C.I. (Pharmaceuticals) at 44s. a phial. A few weeks later it was sold by Glaxo Laboratories at 32s. As a result of negotiations between the interested firms and Allen and Hanburys the price was ultimately fixed at 36s., which was 4s. above the price of the most efficient manufacturer. There was plenty of scope for cutting down expenditure, apart from this amendment.

On a division the new Clause "B" was accepted by 138 to 5.

Foreign Visitors

On a further new clause added by the Lords Mr. BLENKINSOP said it carried out a pledge given to the House of Commons during the Report Stage of the Bill. It empowered Mr. Bevan to make and recover charges for use made of the National Health Service by persons not ordinarily resident in Great Britain, but Mr. Bevan did not intend a general and wholesale exclusion of foreign visitors from the benefits of the scheme.

Mr. WALTER ELLIOT was glad to see an admission that there had been substance in the case previously put forward by the Opposition.

Dr. BROUGHTON pointed out that the Clause would allow a Minister of Health to make charges on all foreigners using the National Health Service. He said Mr. Bevan was unlikely to make such a regulation. Care must be exercised not to discourage people from other countries coming for medical and surgical treatment if they were prepared to pay for it.

The House then agreed to the new Clause, and consideration of the National Health Service (Amendment) Bill concluded.

Questions about Prescribing

Mr. BEVAN gave an assurance on December 8 that he did not intend to levy charges for prescriptions supplied in hospitals, including those supplied in casualty wards.

Also on December 8 Mr. KENNETH ROBINSON asked the Minister of Health if he knew that many doctors in the National Health Service were prescribing patent medicines under their trade names in cases where similar ingredients, if specified in the prescription, could be dispensed at less cost.

Mr. BLENKINSOP, for Mr. Bevan, answered that a committee appointed by the Central and Scottish Health Services Councils was considering this problem.

Epileptics.—On October 17, 1949, there were 14,370 epileptics in England and Wales registered as disabled persons.

Universities and Colleges

UNIVERSITY OF BRISTOL

The Carey Coombs Memorial Prize for 1949 has been awarded to Dr. I. McD. Stewart for an essay on "The Aetiology of Coronary Thrombosis."

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At the annual meeting of the College held on December 1 Sir David K. Henderson was elected President for the ensuing year and Drs. W. A. Alexander, J. D. S. Cameron, T. Douglas Inch, Ian G. W. Hill, James G. M. Hamilton, and A. Colin P. Campbell were elected members of Council. Dr. Alexander was nominated Vice-President.

CONJOINT BOARD OF IRELAND

The following candidates were duly admitted licentiates in medicine and midwifery on December 2, having passed the final examination in medicine, surgery, and midwifery of the Conjoint Board of Ireland: E. Bradley, P. G. Brady, H. D. Coghlan, Jane J. Connolly, L. A. Cullen, J. C. Dillon, J. A. Doherty, Rita D. Dooley, Elizabeth M. Farrell, J. A. Fitzpatrick, J. B. Gallagher, Rhoda P. Kennedy, M. J. Moran, J. E. Murphy, J. R. Murphy, J. A. MacCarthy, Eva T. MacDonald, J. F. McGuire, O. A. McKee, Mary T. McQuaid, J. F. Napier, D. O. Ndukwe, Maeve S. O'Kelly, C. M. Ongley, W. Quirk, B. FitzG. Regan, I. Rosenthal, Catherine T. Tynan, Mary T. Vass, A. M. Wells.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended November 26. [No. 47

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London) (b) London (administrative county). (c) The 16 principal towns in Scotland (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1949					1948 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	32	4	11	2	2	36	5	16	1	—
Deaths		1	—				—	—		
Diphtheria	121	18	28	3	9	141	8	37	4	6
Deaths	1	—	—	—	—	2	—	2	—	—
Dysentery	144	25	88	—	—	72	9	46	2	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	1	—	—	—	—	1	—	—	—	—
Deaths		—					1			
Erysipelas			27	5	3			40	12	4
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				33					37	
Deaths	21	1	8	2	4	21	2	5	3	2
Measles*	1,469	28	39	200	87	8,547	127	197	53	66
Deaths†			—	1	—			—	—	—
Ophthalmia neonatorum	31	3	9	1	—	43	5	10	—	—
Deaths										
Paratyphoid fever	11	1	1 (B)	—	—	1	—	4 (B)	—	—
Deaths	—	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal	710	51	2	2	7	716	63	5	1	2
Deaths (from influenza)‡	35	9	3	—	—	22	2	2	1	—
Pneumonia, primary			266	27				243	32	
Deaths	303	67		11	5	234	29		8	15
Polio-encephalitis, acute	17	1				5	—			
Deaths										
Poliomyelitis, acute	176	23	6	8	1	42	2	2	3	—
Deaths§	21	8				3				
Puerperal fever		—	9				—	9		—
Deaths										
Puerperal pyrexia‖	87	7	6	—	—	82	10	7	—	1
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	2,827	224	365	154	341	1,544	91	281	165	55
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	11	—	1	14	—	3	—	1	4	1
Deaths	—	—	—	—	—	1	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	1,035	43	63	66	67	2,747	162	120	52	16
Deaths	1	—	—	—	—	5	1	—	—	—
Deaths (0–1 year)	288	32	45	23	11	273	29	50	14	13
Deaths (excluding stillbirths)	5,730	995	683	193	148	4,847	779	631	180	120
Annual death rate (per 1,000 persons living)			13·7	12·0				12·7	11·3	
Live births	6,938	1109	867	333	233	7,018	1139	861	327	231
Annual rate per 1,000 persons living			17·4	20·6				17·4	20·5	
Stillbirths	142	16	31			172	12	23		
Rate per 1,000 total births (including stillborn)			35					26		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications in the week ended December 3 were: poliomyelitis 141 (176), polio-encephalitis 15 (17). Figures for the previous week are shown in parentheses.

Multiple cases (poliomyelitis and polio-encephalitis) were reported from the following counties: London 16 (24), Berks 3 (3), Buckingham 2 (5), Chester 2 (6), Essex 7 (16), Gloucester 7 (8), Hertford 2 (6), Kent 10 (14), Lancaster 14 (10), Leicester 3 (7), Middlesex 15 (11), Norfolk 4 (12), Nottingham 6 (5), Oxford 2 (1), Southampton 5 (4), Stafford 5 (3), Surrey 6 (6), East Sussex 4 (3), Warwick 6 (7), West Yorks 19 (17), Glamorgan 6 (5).

National Insurance Figures

The Registrar-General has included in his return for the week ended November 26 a new table which will show, each week, the numbers of claims to sickness benefit made under the National Insurance Act during the last four weeks, with weekly averages for each completed month of the year, in each of the 10 standard regions of England and Wales. The weekly averages so far this year have been highest in the month of March in all regions except the London and South-eastern Region, where the highest month was February, and the Eastern Region, where the figures for those two months were the same. The July averages were the lowest in every region. Figures for England and Wales as a whole were as follows:

Weekly Averages Each Month				Week Ended	
Jan.	157,800	June	83,700	Nov. 22	136,800
Feb.	180,100	July	78,500	Nov. 15	142,300
Mar.	185,400	Aug.	88,900	Nov. 8	135,000
Apr.	114,400	Sept.	100,900	Nov. 1	121,900
May	97,900	Oct.	119,200		

Discussion of Table

In *England and Wales* infectious diseases were more prevalent during the week and there were increases in the notifications of scarlet fever 264, measles 168, whooping-cough 44, acute pneumonia 43, dysentery 28, diphtheria 25, cerebrospinal fever 10, and polio-encephalitis 10. There were falls in the incidence of poliomyelitis 43 and typhoid fever 10.

A small rise in the incidence of scarlet fever occurred in most areas; the largest increases were Yorkshire West Riding 53, London 38, and Derbyshire 36. Increases in the notifications of measles were reported in Durham 63 and Surrey 40, with decreases in Staffordshire 39 and Norfolk 34.

The only change of any size in the notifications of whooping-cough was an increase of 33 in Lancashire. Notifications of diphtheria were the largest for 10 months, with increases in Yorkshire West Riding 7, London 6, and Durham 6.

The largest returns for dysentery were: London 25 (Wandsworth 13); Lancashire 19 (Liverpool C.B. 6, Hindley U.D. 6); Yorkshire West Riding 15 (Leeds C.B. 8, Huddersfield C.B. 6); Durham 15; Gloucestershire 10 (Bristol C.B. 10); Glamorganshire 10 (Cardiff C.B. 6).

In *Scotland* there were increases in the notifications of scarlet fever 96, acute primary pneumonia 50, and whooping-cough 20. An increased incidence of scarlet fever was reported from every area. In Glasgow there was an increase of 52 in the notifications of scarlet fever. The rise in the incidence of pneumonia was contributed mainly by the western area. The chief centres of dysentery were Glasgow 47, Edinburgh 10, and Stirling county 10.

In *Eire* increases were reported in the notifications of measles 149 and whooping-cough 37, while a decrease of 14 was recorded for cases of diarrhoea and enteritis. The rise in the incidence of measles was mainly due to an outbreak of 108 cases in Waterford, Dungarvan R.D. No. 1. The increase in the notifications of whooping-cough was mainly due to 29 cases in Waterford, Mullingar R.D. Of the 14 cases of typhoid 11 were notified in Co. Mayo (Castlebar R.D. 6 and Claremorris R.D. 5).

In *Northern Ireland* the chief feature of the returns was a rise of 65 in the notifications of scarlet fever; an increase of 37 cases was reported in Belfast C.B.

Quarterly Returns for Scotland

During the September quarter the birth rate was equivalent to 17.9 per 1,000, and was 1.0 below the average of the third quarters of the five preceding years. The infant mortality rate was 35 per 1,000 registered live births, which was 5 below the rate for the third quarter of 1948 and 14 below the five years' average. The general death rate at 10.1 per 1,000 was 0.4 below the five years' average.

Deaths attributed to the principal epidemic diseases numbered 34 and included 12 from influenza and 15 from whooping-cough. The death rate from respiratory tuberculosis was 51 per 100,000 and from other forms of tuberculosis 8 per 100,000: these figures were 4 and 5, respectively, below the five-year average.

Week Ending December 3

Notifications of infectious diseases in England and Wales during the week included: scarlet fever 2,755, whooping-cough 981, diphtheria 90, measles 1,654, acute pneumonia 715, cerebrospinal fever 26, acute poliomyelitis 141, acute polio-encephalitis 15, dysentery 159, paratyphoid fever 7, typhoid fever 9, and food-poisoning 121.

Medical News

Nuffield Grant for Cortisone Research

The Nuffield Foundation has made a grant of £5,000 for research on the effects of cortisone in the treatment of rheumatoid arthritis. The research will be carried out under Professor W. T. Astbury, Professor R. E. Tunbridge, and Dr. R. N. Tattersall. As reported last week, the Nuffield Foundation has also made grants to the Universities of Oxford and Cambridge for work on cortisone and allied substances.

Heberden Society Dinner

The annual dinner of the Heberden Society was held at the Royal College of Surgeons on December 9, Dr. W. S. C. Copeman being in the chair. After the loyal toasts had been honoured, Dr. R. M. Mason, in proposing the health of the guests, welcomed Lord Webb-Johnson on his return from the U.S.A. and Canada, and the Heberden orator, Professor F. Wood Jones, F.R.S., who was later presented with the Heberden Medal. Lord Lucas, in replying for the guests, told a cautionary tale about medicine and politics. In proposing the health of the society Lord Webb-Johnson praised Heberden as one of the great clinicians in medical history. Referring to developments of the past decades Lord Webb-Johnson remarked that he had lived long enough to see James Mackenzie lay the foundations of cardiology. In response Dr. Copeman said the medical profession was much indebted to Lord Webb-Johnson for his interest in, and support of those working on, the rheumatic infections. He was glad to be able to say that Lord Webb-Johnson had accepted honorary membership of the society

Bulgaria Leaves WHO

Bulgaria has decided to leave the World Health Organization. It has stated in a letter to WHO that the practical results obtained by WHO "appear completely insufficient, particularly in the field of international health aid." Soviet Russia, the Ukraine, and Byelorussia withdrew from WHO last February (*Journal*, February 26, p. 375).

Visits to North America

It is hoped that any medical men and women who intend to visit North America will inform the Secretary of the B.M.A. so that information of such visits may be forwarded to the Canadian Medical Association, which is anxious to be of help to doctors from the United Kingdom visiting North America.

Fulbright Travel Grants

The United States Educational Commission in the United Kingdom announces that, under the provisions of the Fulbright Programme, travel grants are available to citizens of the United Kingdom and Colonies to go to America for an academic or educational purpose, such as study, research, lecturing, or for other educational activities. Applicants must possess a guarantee of financial support in dollars in America for the proposed period of their stay. Undergraduate and postgraduate students must show proof of admission to an American institution of higher learning. All applicants must be affiliated with such an institution. Applications may be made by candidates who have not yet concluded these financial and institutional arrangements, and in certain rare cases of exceptional merit the commission will try to help obtain dollar support or institutional connexion for those candidates who have not been able themselves to complete these arrangements. Preference will be given to candidates who intend to stay nine months or more, but applications for shorter periods from well-qualified persons who cannot be spared from their present activities for so long will be accepted. Grants cannot be given for attendance at conferences alone. The travel grants are available for travel to America between June 1, 1950, and May 31, 1951. Those wishing to apply should write immediately to the United States Educational Commission in the United Kingdom, 55, Upper Brook Street, London, W.1, requesting a preliminary application card. After return of this completed card the appropriate further forms will be sent to applicants at a later date.

West of England and Wales Society of Dermatology

The inaugural meeting of the West of England and Wales Society of Dermatology was held at Bristol on Friday, October 28. Dr. Clifford D. Evans took the chair. It was decided to hold three clinical meetings each year. One will be held at Bristol in the fourth week of October, one in Wales in the fourth week of January, and one in Gloucester, Plymouth, or Exeter in the fourth week of April. The meeting will be on a Saturday morning and will take the form of a clinical demonstration and discussion followed by lunch. Dr. Robert P. Warin was elected secretary.

Dr. J. McK. A. Lowson

The Sultan of Johore has conferred the decoration of Insignia of the Order of the Crown of Johore upon Dr. J. McK. A. Lowson, Principal Medical Officer, Johore, in recognition of valuable services rendered by him.

A Sixtieth Birthday

The Scandinavian journal, *Acta Tuberculosea Scandinavica*, has recently published a *Supplement* (1949, No. 21) in celebration of Professor Arvid Wallgren's sixtieth birthday. Professor Wallgren, who was for 20 years senior physician at the Children's Hospital, Göteborg, is now professor of child health at the Caroline Institute in Stockholm. The list of his publications contains the titles of 229 papers and books, many on the subject of tuberculosis. The special supplement of *Acta Tuberculosea Scandinavica* contains a number of interesting papers, mostly on the subject of tuberculosis, by Professor Wallgren's Scandinavian colleagues.

Visitors from the U.S.A.

Dr. Harold S. Diehl, dean of the Minnesota School of Medicine, and Dr. L. W. Chandler, dean of the Faculty of Medicine, Stanford University, San Francisco, were guests at a reception held at the Royal Society of Medicine on December 6. They are visiting this country in order to study medical education and its relation to the National Health Service, and they will report their findings to the Council on Medical Education and Hospitals of the American Medical Association. Dr. Diehl and Dr. Chandler hope to return to this country in three or four years' time in order to find out what effect the National Health Service has had on medical education in the intervening period.

COMING EVENTS

Conference on Cardiovascular Diseases

A national conference on cardiovascular diseases will be held in Washington from January 18 to 20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute of the U.S. Public Health Service. Dr. H. M. Marvin and Dr. C. J. Van Slyke, co-chairmen of the conference, have said in a published statement: "This conference we hope will provide the guide-posts for a comprehensive and concrete programme of action to correlate an all-out national attack on the heart disease problem."

Oxford Graduates' Medical Club

The 100th dinner of the Oxford Graduates' Medical Club will be held at the Royal College of Surgeons of England (Lincoln's Inn Fields, London, W.C.) on Friday, January 27, 1950, at 7 p.m. for 7.30 p.m., when the chair will be taken by Dr. C. M. Hinds Howell. Dinner jackets will be worn. Tickets may be obtained from Mr. E. G. Tuckwell, F.R.C.S., 73, Harley Street, London, W.1, price 26s. each. Cheques should be made payable to the Oxford Graduates' Medical Club and should reach Mr. Tuckwell before January 13, 1950.

SOCIETIES AND LECTURES

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, December 20, 5 p.m., "*Common Diagnostic Problems in Renal Disease*," by Professor Clifford Wilson.

INSTITUTE OF DERMATOLOGY, 5, Lisle Street, Leicester Square, London, W.C.—December 20, 5 p.m., "*The Treatment of Varicose Conditions of the Lower Limb*," by Mr. A. K. Monro.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 20, 3.45 p.m., "*The Larynx*," Arnott Demonstration by Mr. R. J. Last.

APPOINTMENTS

T. P. Mann, M.D., M.R.C.P., D.C.H., has been appointed Assistant to the Professor of Child Health at the Institute of Child Health, University of London, from November 1, 1949.

Dr. Mann will work in the Newborn Baby Department at the Postgraduate Medical School of London, Ducane Road, Hammersmith. He qualified at St. Mary's Hospital in 1941, and after serving as surgeon lieutenant in the R.N.V.R during the war was medical registrar at the Postgraduate Medical School.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Consultant Ear, Nose, and Throat Surgeon in Peterborough Area*, A. A. Finlayson, F.R.C.S. *Consultant Radiologist in King's Lynn Area*, Group Captain G. E. Church, M.B., Ch.B., D.M.R., D.M.R.E., R.A.F.

HINDE, R. T., F.R.C.S., Assistant Ear, Nose, and Throat Surgeon, Exeter Clinical Area, South-Western Regional Hospital Board.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Burslem.—On November 30, 1949, at the City Hospital, Chester, to Kathleen (née Griffiths), wife of R. W. Burslem, M.D., M.R.C.O.G., a son.

Harris.—On November 11, 1949, at Nairobi, Kenya, East Africa, to Dr. L. B. Mary Harris (née Watch), wife of Norman Francis Harris, a son.

Heanley.—On November 26, 1949, to Molly, wife of Charles Laurence Heanley, F.R.C.S., a third son.

Hughes.—On December 3, 1949, at Klinik Hirslanden, Zurich, Switzerland, to Joy (née Laxton), wife of Dr. D. R. Hughes, a son—Christopher Dennis.

Tarnesby (formerly Tarnowski).—On November 28, 1949, at 6, Downside Crescent, Hampstead, London, N.W., to Eleanor (née Ettlinger), L.M.S.S.A., and Herman P. Tarnesby, M.B., B.S., D.R.C.O.G., a daughter—Ruth Marie Bettina Tamara.

DEATHS

Braterman.—On December 3, 1949, at 267, Ealing Road, Wembley, Middlesex, Harry Lewis Braterman, M.R.C.S., L.R.C.P., aged 43.

Gavin.—On December 4, 1949, at his home, William Christopher Gavin, M.B., B.Ch.

Jones.—On December 3, 1949, at Northgate, Russell Road, Rhyl, Flintshire, Edward Hughes Jones, M.D., J.P., aged 84.

Jones.—On December 3, 1949, at 1, Grasmere Avenue, Whitefield, Manchester, John Grant Jones, M.D., late of Birnie, Elgin, Moray, aged 77.

McDonald.—On December 6, 1949, at Belford Villa, Belford, Northumberland, James McDonald, M.D., J.P., aged 82.

MacFaul.—On December 7, 1949, at his residence, Claremont, St. Helens Road, Leigh, Lancs, Alexander MacFaul, M.B., B.Ch.

McKinstry.—On December 7, 1949, William Kilbourn McKinstry, M.R.C.S., L.R.C.P., aged 50.

Munro.—On December 8, 1949, in London, Hector Munro, M.B., C.M., of 9, Queen Anne Street, London, W.1.

Ogg.—On December 5, 1949, at 1, Briardale Gardens, Hampstead, London, N.W., Theodore Alexander William Ogg, M.D.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Pulmonary Tuberculosis

Q.—*(1) I should be grateful for information about pneumoperitoneum and its advantages over other methods of collapse therapy, with special reference to phrenic nerve operations. How soon can a pneumoperitoneum be started, and what are the risks and contraindications? (2) What improvement may occur in tuberculous women as a result of pregnancy?*

A.—(1) The fullest information available about pneumoperitoneum is contained in A. L. Banyai's *Pneumoperitoneum Treatment*, published in 1946. Many physicians would consider that this presents a rather too enthusiastic view of the part played by this form of treatment in pulmonary tuberculosis. A very adequate, though less full, general account of artificial pneumoperitoneum in pulmonary tuberculosis will be found in the second edition of Kayne, Pagel, and O'Shaughnessy's *Pulmonary Tuberculosis*, edited by Pagel, Simmonds, MacDonald, and Fatti (1948). Only a few general observations can be made here. Pneumoperitoneum is best regarded as an adjunct to phrenic paralysis; unless the diaphragm is made rigid by old inflammatory changes, especially pleural, pneumoperitoneum allows the paralysed diaphragm to rise very high in the chest and thus effect selective relaxation of one lung. This relaxation is less complete than that obtained by a good artificial pneumothorax, but the possible pleural complications of pneumothorax are of course avoided. The treatment of recent acute tuberculous lesions by artificial pneumothorax leads to a high incidence of serous pleural effusions and empyemata; even if these are eventually absorbed they lead to gross pleural thickening and consequent serious diminution of pulmonary function. Hence in the treatment of such acute cases artificial pneumothorax is now generally avoided. Phrenic paralysis and pneumoperitoneum, however, can be instituted immediately without giving rise to the risks associated with pleural reactions. Hence these acute cases with predominantly unilateral disease form an important indication for pneumoperitoneum and phrenic paralysis. In such cases pneumoperitoneum should be regarded as probably only a preliminary to some further form of treatment. Phrenic paralysis and pneumoperitoneum may also be used as an adjunct to rest in bed in the treatment of less acute and less extensive lesions.

The only positive contraindications to pneumoperitoneum likely to be encountered are active tuberculous peritonitis and the presence of old peritoneal adhesions from any cause. Complications include air embolism, which seems to be nearly as frequent as in artificial pneumothorax; peritoneal effusion, which is very much rarer than pleural effusion in artificial pneumothorax and probably occurs in no more than 1 or 2% of cases; the accidental induction of pneumothorax if the pneumoperitoneum refills are given through the lowest intercostal space; pneumomediastinum; and the production of herniae in the usual hernial orifices, probably because of the increase in intra-abdominal pressure.

(2) This question also is difficult to answer briefly. It was the opinion of French physicians in the latter half of the nineteenth century that pregnancy actually benefited tuberculous women, and many physicians would agree that during pregnancy the general condition of tuberculous women often improves considerably. On the other hand, obstetricians take a gloomy view of the fate of the tuberculous woman after delivery; and physicians in general would agree that it is in the months after delivery that relapses of tuberculous disease tend to occur. Such statistical evidence as is available indicates that no ultimate difference in result will be found in comparable groups of tuberculous women who have borne children and of those who have not. This suggests that the slight improvement which occurs during pregnancy is offset by the greater tendency to relapse in the months after delivery. Certainly there is no statistical evidence to justify routine termination of pregnancy in tuberculous women. Recent papers worth consulting on this point include those by Stewart and Simmonds (*British Medical Journal*, 1947, **2**, 726), Cohen (*Brit. J. Tuberc.*, 1946, **40**, 10), and Friedman and Garber (*Amer. Rev. Tuberc.*, 1946, **54**, 275).

Lymphocytosis in Whooping-cough

Q.—*A relative and pronounced lymphocytosis is an outstanding feature of an attack of whooping-cough. Is there any relationship between the severity of the attack and the degree of lymphocytosis? Is an injection of whooping-cough vaccine followed by lymphocytosis?*

A.—A leucocytosis with lymphocytosis (over 60%) is a characteristic response in whooping-cough, but no satisfactory explanation for its occurrence has yet been given. The lymphocytosis is most marked in the paroxysmal and whooping stages of the infection. It may be absent in infants under 6 months of age and, as infection is often very severe in infancy, the lymphocytic response cannot be regarded as a prognostic sign. Very high leucocyte counts, up to 100,000 or more per c.mm., are often found in cases with complications, such as bronchopneumonia, in which the total lymphocyte count may reach 60,000 per c.mm., but here the secondary bacterial infection may be an added stimulus. A lymphocytic response of varying degree to pertussis vaccine has been reported by Sauer (*J. Amer. med. Ass.*, 1933, **100**, 239) to occur in some 60% of young children after two or three injections of vaccine.

Causes of Death

Q.—*(a) What are the commonest killing diseases in adults in order of frequency? (b) What groups of diseases—for example, cardiovascular, respiratory, alimentary, etc.—are responsible for most deaths, and has there been any change in the last 50 years?*

A.—*(a)* The numerical importance of a cause of death depends on the sex and the period of life considered. The most important causes of death for three broad age groups for the most recent triennium available are:

Actual Number of Deaths, 1945–7

Cause	Males					
	20–39 Years		40–59 Years		60 Years and Over	
	No.	% of All Causes	No.	% of All Causes	No.	% of All Causes
Tuberculosis ..	12,189	31·98	16,115	11·18	7,329	1·48
Cancer	3,083	8·09	29,658	20·58	78,666	15·88
Intracranial lesions of vascular origin ..	461	1·21	8,715	6·05	60,645	12·24
Heart diseases ..	3,625	9·51	30,151	20·92	166,629	33·63
Bronchitis	914	2·40	10,820	7·51	39,808	8·04
Pneumonia	1,175	3·08	5,662	3·93	15,931	3·22
Nephritis	1,496	3·92	4,300	2·98	12,909	2·61
Violence	6,624	17·38	9,506	6·60	12,149	2·45
	Females					
Tuberculosis.. ..	14,585	35·31	5,735	5·35	2,387	0·46
Cancer	4,229	10·24	33,791	31·49	76,114	14·81
Intracranial lesions of vascular origin ..	611	1·48	11,117	10·36	82,809	16·11
Heart diseases ..	4,369	10·58	18,915	17·63	180,779	35·18
Bronchitis	627	1·52	3,459	3·22	29,953	5·83
Pneumonia	1,187	2·87	3,072	2·86	15,149	2·95
Nephritis	1,441	3·49	3,909	3·64	12,758	2·48
Violence	2,557	6·19	4,330	4·04	11,839	2·30

(b) The second part of this question presents some difficulties. The fall in the death rates in each age group during the past 50 years has considerably modified the age structure of the population and the risk of dying from specific causes. Owing to the changes in classification and tabulation that have been made during this period because of the increase in medical knowledge a comparison of deaths over a series of years up to 1940 is open to objections. The introduction in 1940 of the

physician's preference when two causes are associated makes it impossible to compare the present classification with that of earlier years. A comparison of the deaths in 1931 with those in 1947, the longest series that can safely be used, is as follows:

Disease	1947		1931	
	No. of Deaths	% of All Causes	No. of Deaths	% of All Causes
Tuberculosis	23,075	4·5	34,959	7·1
Cancer	79,706	15·5	60,162	12·2
Diseases of the nervous system	65,458	12·7	50,781	10·3
Diseases of circulatory system ..	164,015	31·8	103,268	21·0
Diseases of respiratory system ..	60,740	11·8	80,279	16·3
Diseases of digestive system ..	21,044	4·1	25,785	5·2
Diseases of urinary system ..	20,411	4·0	25,354	5·2
Violence	19,826	3·8	21,395	4·4
Other causes	61,316	11·9	89,647	18·2
All causes	515,591	100	491,630	100

The crude death rate in both years was 12.3 per 1,000. The changes in the relative importance of the various groups of diseases, especially those which are the most frequent cause of death in old age, have been largely due to the decrease in the death rates throughout life, which has resulted in more people living to older ages than formerly.

Vitamin D_2 for Chilblains

Q.—*For the past four or five years I have been using ampoules of calciferol containing 600,000 i.u. of vitamin D_2 with great success in the treatment of chilblains, so far without any ill effects. I gave six ampoules—one each week. Recently I have been told that there is danger of calcification of the renal tubules with this treatment. Is this correct, and is the danger great enough to warrant stopping the treatment? Calciferol dragees, each containing 50,000 i.u. of vitamin D_2, are also obtainable. Would treatment by these be free from risk, and what dosage should be used?*

A.—A dose of 600,000 i.u. of vitamin D_2 per week is approaching an amount which can produce toxic symptoms. These may appear with a dose of 100,000 units daily. The use of large doses of vitamin D_2 is not free from risk, the chief results of overdosage being hypercalcaemia with calcification of the kidneys and blood vessels, anorexia, lassitude, headache, and albuminuria. *No controlled observations have been made to show that vitamin D is effective in the treatment of chilblains, and to use a drug in toxic doses for this purpose is hardly justified.* The rationale for the use of vitamin D in the treatment of chilblains rests on the false assumption that a raised blood calcium level will decrease capillary permeability, which may be increased in patients with chilblains. The prolonged use of doses of 50,000 units or more of vitamin D a day is justified only in the treatment of lupus vulgaris, and then it should be controlled by blood calcium estimations.

Boils in Ear

Q.—*How should a case of recurrent boils in the ear be treated?*

A.—Recurrence of boils in the ear may be due to general or local causes. Such diseases as diabetes and nephritis must therefore be excluded. Carbohydrate intake should be reduced, and a varied and well-balanced diet is important. Locally, care must be taken that cross-infection of the meatal wall is avoided, and that a chronic dermatitis does not result from the acute stage. A wick soaked in magnesium sulphate paste, which is generally preferable to aluminium acetate, will help. For some weeks after the acute stage is over the meatus should be mopped out with spirit 75%, or 2% gentian violet in spirit. If a chronic dermatitis is present it should be treated on the usual lines—as, for example, with linimentum calaminae. Various measures may be tried to raise the bodily resistance to staphylococcal infection, but the results are often poor. Ultraviolet-light baths to the whole body two or three times a week for four weeks have been advised by some authorities. The questioner might also refer to the article by W. M. Mollison which appeared in the *Journal* of October 22 (p. 923).

NOTES AND COMMENTS

Estimation of Erythrocyte Sedimentation Rate.—Dr. JAMES KELMAN (Perth) writes: In "Any Questions?" (November 12, p. 1127), in answer to the query whether flocculation should occur in the 3.8% citrate solution (taking this to refer to the blood-citrate mixture), it is stated that "if gross agglutination or flocculation occurs then either the blood has started to clot or the patient is suffering from gross hyperglobulinaemia, the most common cause of which in this country is myelomatosis." Granularity of the sedimenting cells is not infrequently to be found in any very rapidly sedimenting blood, but it has to be looked for. Using a micro-method which involves mixing citrate and blood on a cell slide, I have seen flocculation occurring on the slide on a number of occasions in blood from persons in the acute stage of severe scarlet fever and also in cases of active pulmonary tuberculosis. Balachowsky, S. (*Rev. méd. Suisse rom.*, 1923, **43**, 714), drew attention to this phenomenon, and declared it to be of bad prognosis. This was certainly not so in my scarlet fever cases, all of whom made a good recovery, but in the tuberculosis cases the longest period of survival was six months. The effect of tilting the tube, also mentioned in your reply under this heading, can be very marked. Wintrobe, M. M., and Landsberg, J. W. (*Amer. J. med. Sci.*, 1935, **189**, 102), state that even a difference of two or three degrees may accelerate sedimentation up to 30%. It is interesting however to note that Balachowsky in an earlier article (*Bull. Mém. Hôp. Paris*, 1925, **49**, 1141) showed that quick results could be obtained by using a stand which fixed the tubes at an angle, but this method does not appear to have found favour.

High-pitched Voice in Adult Male.—Dr. VERNON O'HARA-CUSSEN (Cork, Ireland) writes: The reply given to the question on high-pitched voice in adult male ("Any Questions?" November 26, p. 1246) is incomplete. It is doubtful if in ordinary practice hormone deficiency is ever more than an accessory factor in producing the falsetto voice. In normal voice production the larynx is pulled downwards by the sterno-thyroid and sterno-hyoid muscles for low-pitched sounds. For high-pitched sounds the use of the supra-hyoid muscles is necessary. Men with falsetto and "pressor" voices use the latter set of muscles almost entirely for all sounds. By training such individuals to use the infra-hyoid muscles to draw down the larynx the required change of tone in the voice can usually be readily and permanently attained.

Intranasal Oil.—Dr. GEORGE W. C. JOHNSON (Harrogate) writes: The intranasal use of oily preparations was mentioned in "Any Questions?" (November 26, p. 1245). It is pertinent to add to the answer printed a reference to the possible danger of "lipoid-cell pneumonia" following the use of these substances. When a student in America a few years ago I was taught that oily preparations can be hazardous, especially for small children, if given intranasally. I have not myself seen any patients adversely affected, but perhaps I may mention the section on lipoid-cell pneumonia in *Cecil's Text-book of Medicine* (1947, p. 142, Philadelphia) and also the abstract (No. 1846 in *Abstracts of World Medicine* for October, 1949) of a paper by Schneider (*New Engl. J. Med.*, 1949, **240**, 284) concerning mineral oil in the lungs.

Copra Bug.—Mr. JOHN A. FREEMAN, Ph.D. (Chief Entomologist, Ministry of Agriculture and Fisheries), writes: May I refer to the reply to the first item of "Any Questions?" for October 22 (p. 939)? I think it is incorrect to state that the "copra bug" is to be identified with the mite *Tyrophagus castellani*. The insect commonly known as the "copra bug" is the Clerid beetle, *Necrobia rufipes* DeGeer, which is often very common on cargoes of copra and other "oil-seeds." Although it is frequently accused by dockers of biting, there does not appear to be any evidence that it can do so. The irritation resulting from the handling of copra and other infested conditions is, as your reply states, properly attributed to the presence, at some time, of the particular mite.

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